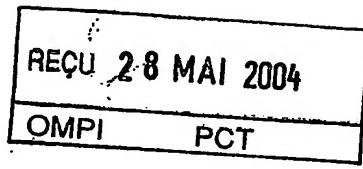




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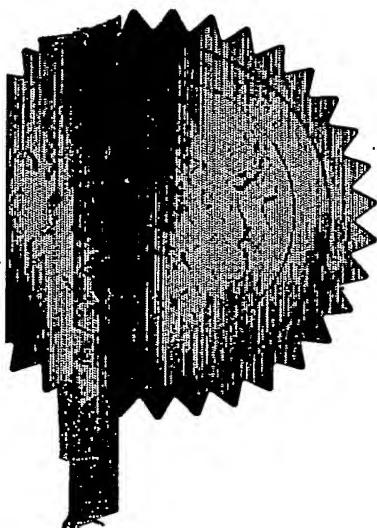
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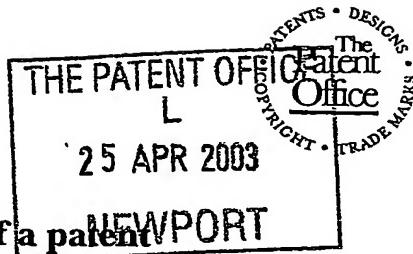
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1. Your reference

P15823-GB

2. Patent application number

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3. Full name, address and postcode of the or of each applicant (*underline all surnames*)

ELI LILLY AND COMPANY,
LILLY CORPORATE CENTER,
INDIANAPOLIS,
INDIANA 46285, USA

Patents ADP number (*if you know it*)

428904002 ✓

If the applicant is a corporate body, give the country/state of its incorporation

STATE OF INDIANA, U.S.A.

4. Title of the invention

QUINOLONE DERIVATIVES

5. Name of your agent (*if you have one*)

KINGSBURY, Oliver William

"Address for service" in the United Kingdom to which all correspondence should be sent (*including the postcode*)

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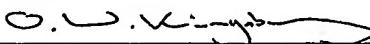
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Notes

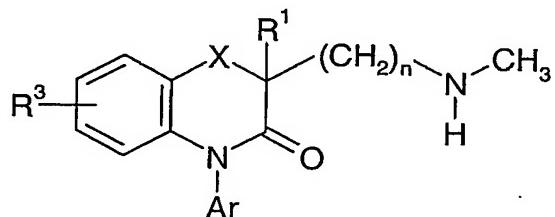
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QUINOLONE DERIVATIVES

This invention relates to novel quinolone compounds, and to their use in selectively inhibiting norepinephrine reuptake.

5 Selective inhibition of norepinephrine reuptake is a relatively new mode of action for the treatment of affective disorders. Norepinephrine appears to play an important role in the disturbances of vegetative function associated with affective, anxiety and cognitive disorders. Tomoxetine hydrochloride is a selective inhibitor of norepinephrine, and is marketed for the treatment of attention deficit
 10 hyperactivity disorder (ADHD). Reboxetine is a marketed selective norepinephrine reuptake inhibitor for the treatment of depression.

According to the present invention there is provided a compound of formula (I)



(I)

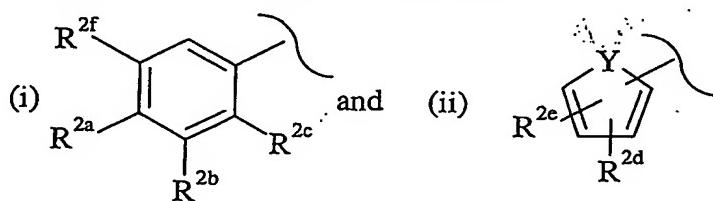
wherein

-X- is -C(R⁴R⁵)-, -O- or -S-;

n is 2 or 3;

R¹ is H or C₁-C₄ alkyl;20 R³ is H, halo, C₁-C₄ alkyl, O(C₁-C₄ alkyl), nitrile, phenyl or substituted phenyl;R⁴ and R⁵ are each independently selected from H or C₁-C₄ alkyl;

Ar- is selected from the group consisting of





in which

R^{2a} is H, halo, methyl or ethyl;

R^{2b} is H, halo or methyl;

5 R^{2c} is H, halo, methyl, trifluoromethyl, nitrile, or methoxy;

R^{2d} is H, halo, methyl or ethyl;

R^{2e} is H, halo, methyl, trifluoromethyl, nitrile, or methoxy;

R^{2f} is H, or fluoro;

-Y- is -O-, -S- or -N(R⁶)-; and

10 R⁶ is H or methyl

and pharmaceutically acceptable salts thereof.

The term "C₁-C₄ alkyl" as used herein includes straight and branched chain alkyl groups of 1, 2, 3 or 4 carbon atoms. Thus the term "C₁-C₄ alkyl" includes 15 methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. C₁-C₂ alkyl groups are preferred. A particularly preferred C₁-C₄ alkyl group is methyl or ethyl.

The term "halo" includes F, Cl, Br and I, and is preferably F or Cl.

The term "substituted phenyl" means phenyl substituted with 1, 2, 3, 4 or 5 20 substituents, preferably with 1 or 2, for example 1, substituent. Suitable substituents include C₁-C₄ alkyl, O(C₁-C₄ alkyl), S(C₁-C₄ alkyl), halo, and phenyl optionally substituted with, for example, C₁-C₄ alkyl, O(C₁-C₄ alkyl), S(C₁-C₄ alkyl), or halo.

The terms "O(C₁-C₄ alkyl)" or "S(C₁-C₄ alkyl)" mean a C₁-C₄ alkyl group 25 as defined above linked to the point of substitution via an oxygen or a sulphur atom. An O(C₁-C₄ alkyl) or S(C₁-C₄ alkyl) group includes for example methoxy, ethoxy, thiomethyl or thioethyl.

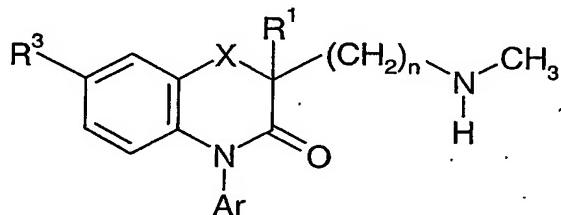
The present invention includes the pharmaceutically acceptable salts of the 30 compounds of formula (I), formula (Ia) or formula (II). Suitable salts include acid addition salts, including salts formed with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic

acids, such as organic carboxylic or organic sulphonic acids, for example, acetoxybenzoic, citric, glycolic, mandelic-l, mandelic-dl, mandelic-d, maleic, mesotartaric monohydrate, hydroxymaleic, fumaric, lactobionic, malic, methanesulphonic, napsylic, naphthalenedisulfonic, naphtoic, oxalic, palmitic, 5 phenylacetic, propionic, pyridyl hydroxy pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric-l, tartaric-dl, tartaric-d, 2-hydroxyethane sulphonic, toluene-p-sulphonic, and xinafoic acids.

In addition to the pharmaceutically acceptable salts, other salts may serve as intermediates in the purification of compounds or in the preparation of other, for 10 example pharmaceutically acceptable, acid addition salts, or are useful for identification, characterisation or purification.

It will be appreciated that compounds of formula (I), formula (Ia) and formula (II) possess asymmetric carbon atoms, and that in the present invention specific individual stereoisomers are preferred.

15 A preferred group of compounds according to the present invention is represented by the formula (Ia)



(Ia)

wherein -X-, n, R¹, R³ and Ar have the values as defined for formula (I)

20 above.

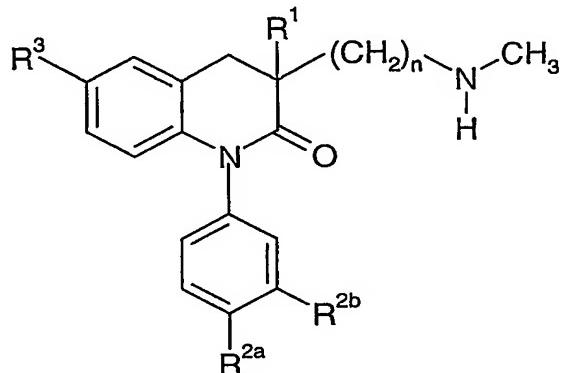
All the compounds of formulae (I) and (Ia) are embodiments of the present invention, but compounds wherein -X- is -C(R⁴R⁵)- are preferred. Even more preferred are compounds wherein -X- is -C(R⁴R⁵)- and R⁴ and R⁵ are both H or R⁴ and R⁵ are both the same C₁-C₄ alkyl.

25 As mentioned above, all the compounds of formulae (I) and (Ia) above are embodiments of the present invention, but compounds wherein Ar is (i) are also preferred. Preferably Ar is (i) and R^{2c} is H. Even more preferred are compounds

wherein Ar is (i), R^{2c} is H, and (a) R^{2a} is H or methyl, R^{2b} is H and R^{2f} is H or (b) R^{2a} is H, R^{2b} is halo, preferably fluoro or chloro and R^{2f} is H or fluoro.

Another group of preferred compounds of the invention are compounds wherein Ar is (ii) and -Y- is -S-. More preferably Ar is 2-thiophenyl or 3-thiophenyl.

5 A further preferred group of compounds according to the present invention is represented by the formula (II)



(II)

wherein

10 n is 2 or 3;

R¹ is H or C₁-C₄ alkyl;

R³ is H, halo, phenyl or substituted phenyl;

R^{2a} is H, halo, methyl or ethyl;

R^{2b} is H, halo or methyl; and pharmaceutically acceptable salts thereof.

15

It will be appreciated that all the compounds of formulae (I), (Ia) and (II) are embodiments of the present invention, but certain compounds are preferred.

Preferably n is 3.

Also preferably R¹ is H, methyl, ethyl or n-propyl.

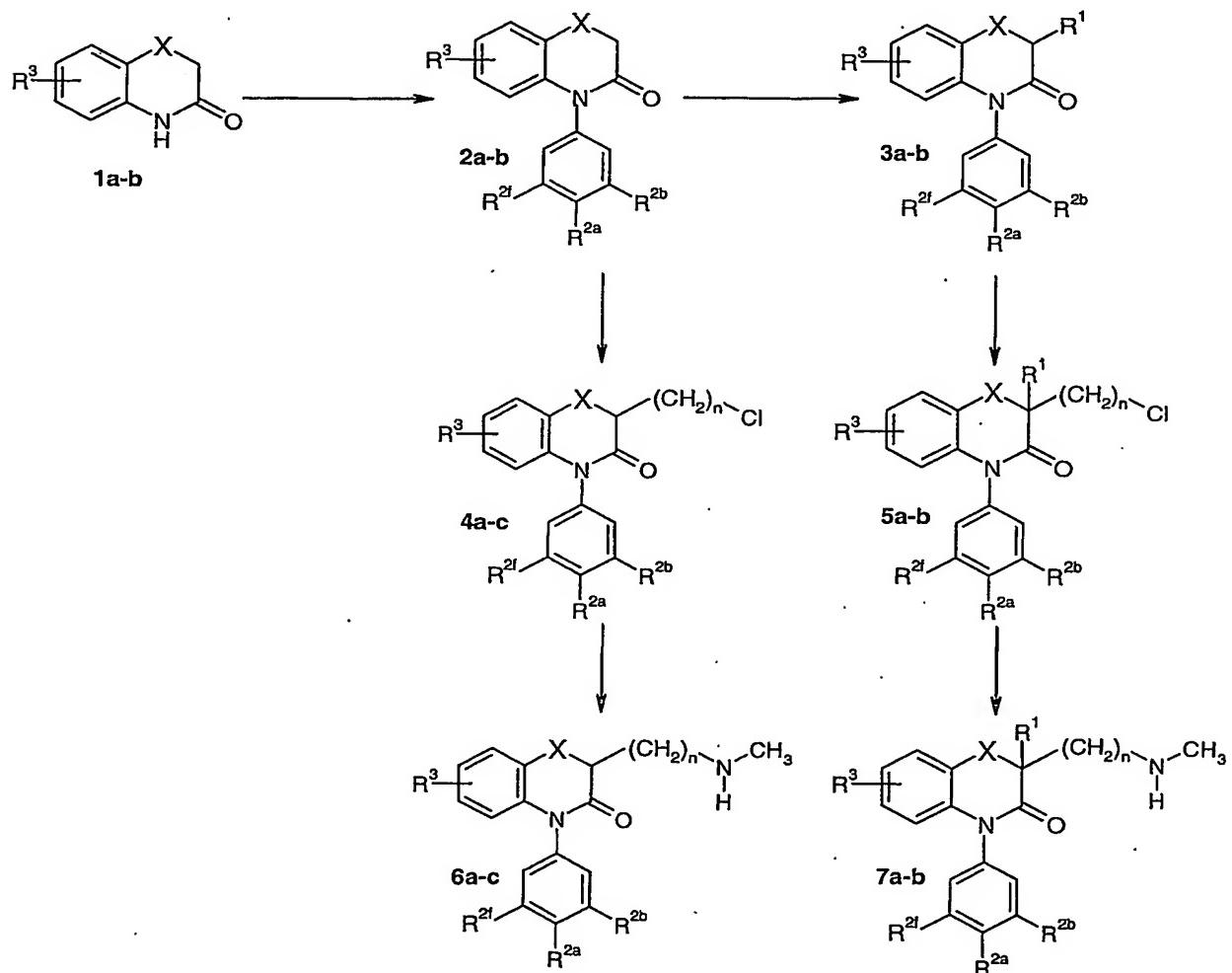
20 It is also preferred that R³ is H or halo.

Compounds of the present invention may be prepared using the following methods. General schemes outlining the synthetic routes used to prepare racemic products are given below. All active racemates were separated into single

enantiomers using chiral HPLC and in most cases the enantiomers were converted into D-tartrate salts.

Compounds of formula (I) wherein Ar is (i) and R^{2c} is H may be prepared as
5 shown in method A below.

Method A



Scheme 1

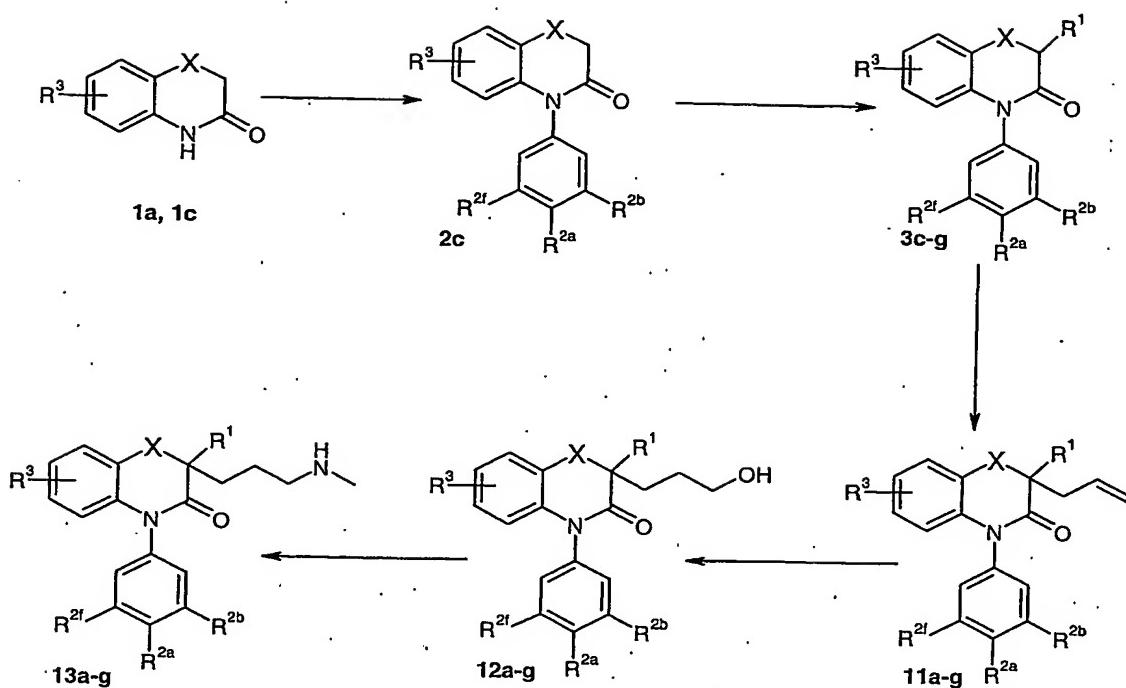
10 Quinolin-2-one (**1**) or its corresponding 4-oxo and 4-thio derivatives can be
N-arylated using modified conditions to those reported by Buchwald, (*J. Am. Chem.
Soc.*, 123, 2001, p. 7727). For example the quinolin-2-one (**1**) is reacted with 3

equivalents of Ar-Br wherein Ar is (i) and R^{2c} is H, 0.2 equivalents of trans-cyclohexanediamine, 0.2 equivalent of copper iodide (CuI), 2.1 equivalents of potassium carbonate (K₂CO₃), in an organic solvent such as 1,4-dioxane at a temperature of 125°C overnight. The resulting N-arylated quinolin-2-one (2) can be
5 alkylated by treatment with a strong base such as lithium hexamethyldisilazide (LiHMDS) at temperatures of -78°C in a suitable organic solvent such as tetrahydrofuran (THF), followed by the addition of an alkyl halide such as alkyl iodide to give the corresponding 3-alkylated-N-arylated quinolin-2-one derivative (3). Using the same alkylating conditions above with a 1,2-dihaloethane, such as
10 1-bromo-2-chloroethane, or a 1,3-dihalopropane, such as 1-bromo-3-chloropropane, as alkylating agents provides (4) or (5) wherein n is 2 or 3 respectively. These halo analogues were chosen as ideal precursors to the desired amine products. For instance, treatment of (4) or (5) with aqueous methylamine, in the presence of a catalytic amount of a suitable iodide, such as potassium iodide (KI), in ethanol at
15 100°C provided the racemic amine products (6) and (7) respectively, in moderate yields.

Compounds of formula (I) wherein Ar is (i), R^{2c} is H and n is 3 may be prepared using alternative method B.

20

Method B



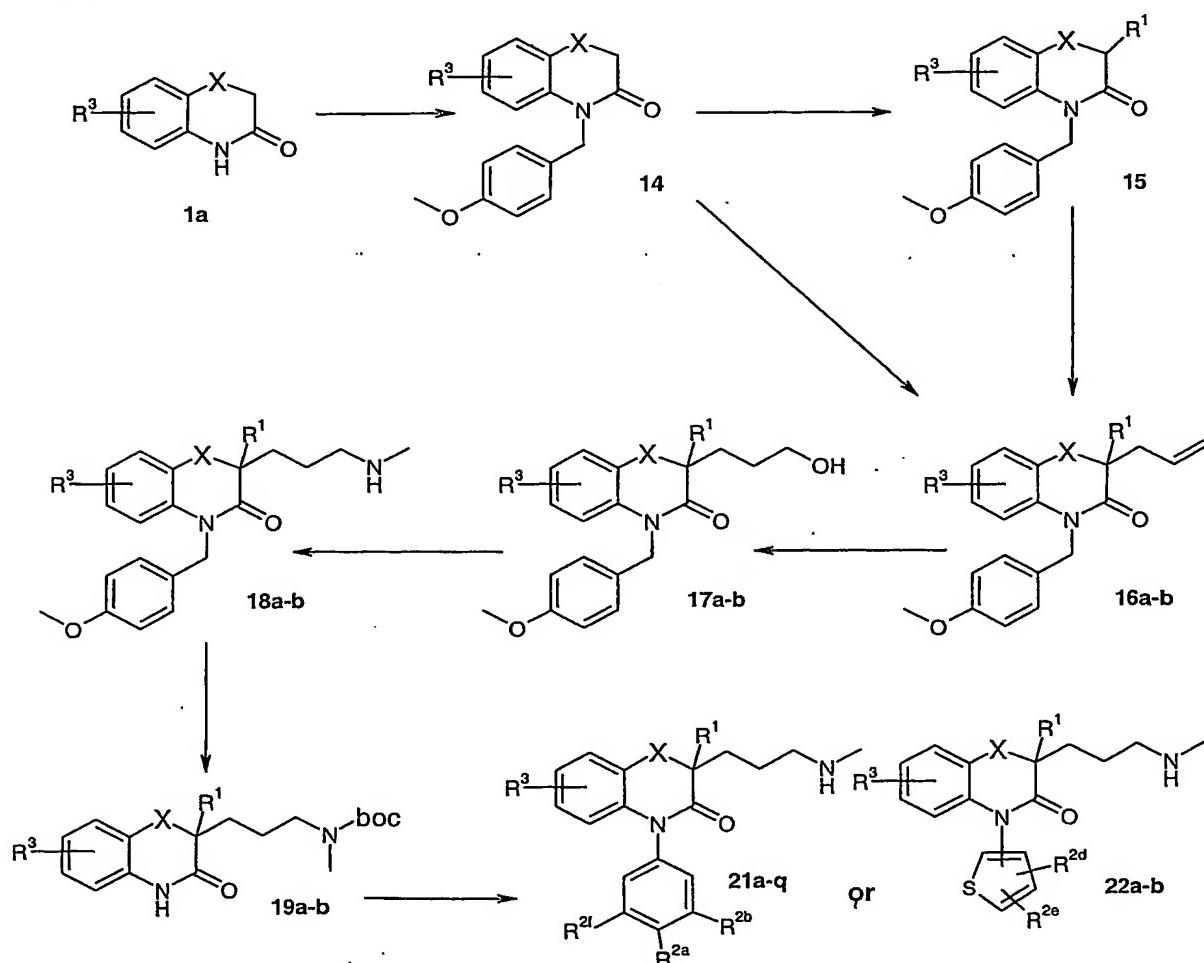
Scheme 2

5

Quinolin-2-ones (2) and (3) can be alkylated using the aforementioned alkylating procedure using an allyl halide e.g. allyl bromide as the alkylating agent to give the corresponding 3-allyl-N-arylated-quinolin-2-ones (11a-g). Said allyl analogues could then be converted to the corresponding primary alcohols (12a-g) by a hydroboration procedure involving a suitable borane, such as 9-BBN in a suitable solvent such as THF. Oxidative work up using for example reaction conditions such as aqueous hydrogen peroxide in a solvent such as ethanol, in the presence of a suitable base, such as sodium hydroxide, gave moderate to good yields of alcohol products after column chromatography purification. The alcohols were cleanly converted into their mesylates, by reaction of a mesyl halide such as mesyl chloride in the presence of a suitable base such as triethylamine in a suitable solvent such as THF at a suitable temperature such as 0°C to room temperature. The resulting mesylates are used directly in the amination step described above in method A to provide good yields of the final racemic targets (13a-g).

In order to prepare a range of N-arylated analogues advanced intermediates were prepared that could undergo N-arylations with a range of substituted aryl halides, such as aryl bromides or iodides, 2 and 3-halothiophenes, 2 and 3-halofurans or 2 and 3-halopyrroles (Method C). The synthetic route used to prepare intermediates (**19a-b**) is shown below (Scheme 3).

Method C



10

Scheme 3

Compounds of formula (I) wherein n is 3 may be prepared as shown in method C. This method is particularly suitable for compounds wherein Ar is (i) and R^{2c} is H or Ar is (ii), wherein -Y- is -S-.

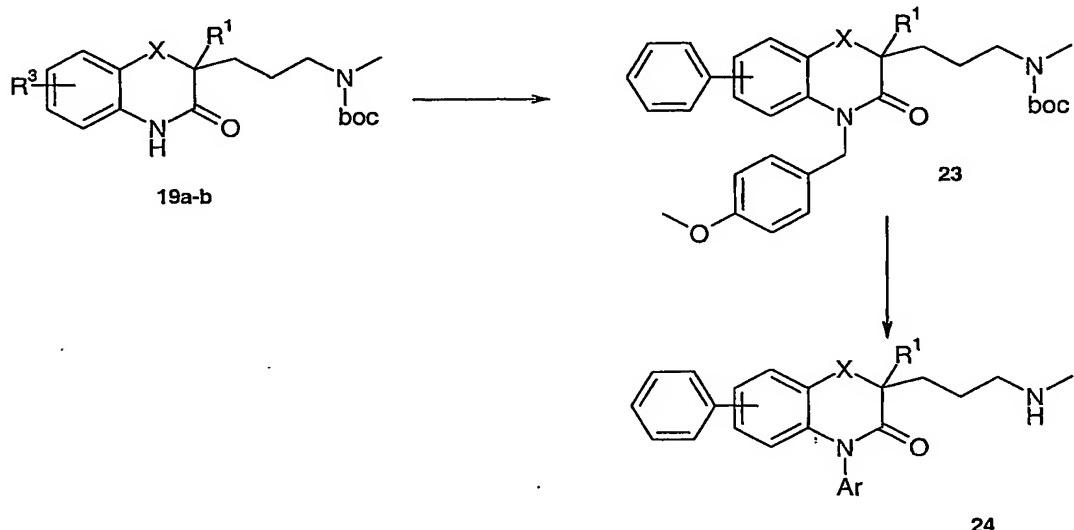
- 5 Quinolin-2-one (1) can be protected using a suitable amide-protecting group as those described in T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1991, hereafter referred to as "Greene". For example quinolin-2-one (1) can be protected with a 4-methoxybenzyl group. The protection reaction can be carried out for example using a suitable base, such as 10 sodium hydride in a suitable solvent, such as dimethylformamide, followed by reaction with a 4-methoxybenzyl halide, such as 4-methoxybenzyl chloride, to give the corresponding N-protected derivative (14) in good yield. This intermediate can be converted directly to the allyl analogue (16a), wherein R¹ = H, in a manner described earlier or converted into the alkyl analogue (15) which can be 15 subsequently alkylated with a allyl halide to give the allyl analogue (16b), wherein R¹ is C₁-C₄ alkyl. Using the same hydroboration, mesylation and amination sequence described in Method B provided both amines (18a-b). Deprotection of protected quinolin-2-one could be achieved using any suitable deprotection conditions as those shown in Greene. For example, the 4-methoxybenzyl group 20 could be cleaved cleanly using trifluoroacetic acid and anisole at 65°C. The resultant product could be selectively protected on the secondary amine with a suitable nitrogen protecting group as those described in Greene. For example, the secondary amine can be protected with a Boc group. The reaction can be carried out with Boc anhydride in a suitable solvent such as THF to provide multi gram quantities of 25 (19a-b). Reaction of (19a-b) with various aryl bromides using the previously described N-arylation conditions, deprotection using suitable deprotecting conditions such as those described in Greene gave a range of final racemic targets (21a-q or 22a-b). For example, for compounds protected with a Boc group they can be deprotected in the presence of trifluoroacetic acid (TFA) in a suitable organic 30 solvent such as dichloromethane (DCM).



Intermediates (**19 a-b**) wherein R³ is a halo group, for example chloro or bromo, can be used to provide compounds of formula (**I**) wherein R³ is a phenyl group, such as compound (**24**), via a Suzuki coupling, see scheme 4 below.

5

Method D



Scheme 4

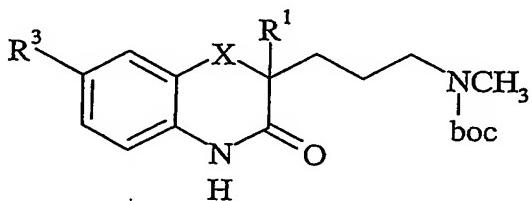
Intermediates (**19a-b**), wherein R³ is for example bromo can be N-protected
10 with a suitable amide protecting group for example 4-methoxybenzyl as described
in method C above and then coupled with phenylboronic acid under Suzuki
conditions to provide the phenyl analogues (**23**). Deprotection of the 4-
methoxybenzyl group with TFA, followed by protection of the resulting secondary
15 amine with a suitable nitrogen protecting group such as Boc followed by subsequent
N-arylation and Boc deprotection using the previously described methodology gave
the final target (**24**).

It will be appreciated that compounds of formula (**Ia**) wherein R³ is bromo
or chloro can be prepared as shown in methods A to D above starting from the
20 corresponding haloquinolin-2-ones. Alternatively, they can be prepared from the
corresponding quinolin-2-one (**1a**) wherein R³ is hydrogen as mentioned above
including an extra step comprising the halogenation of a suitable intermediate at

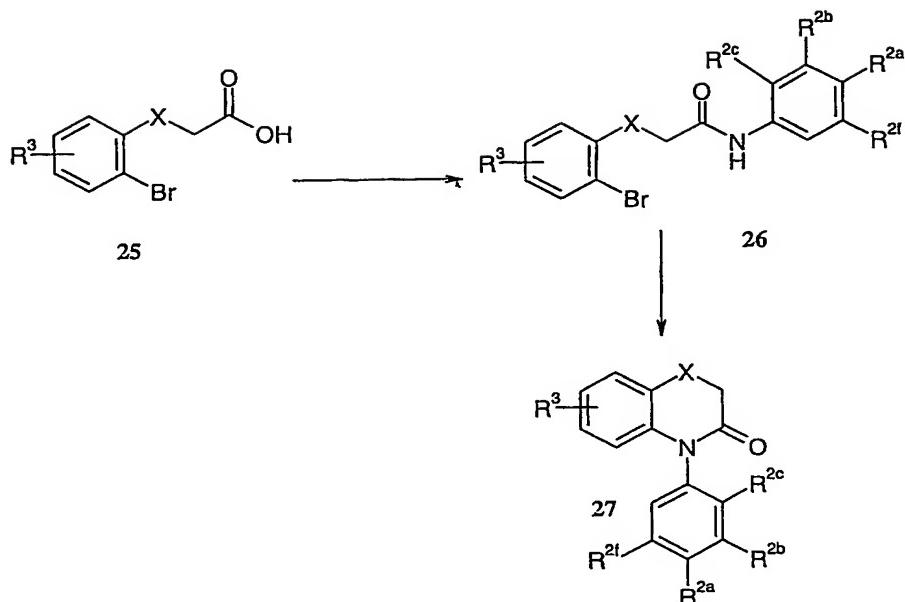
some stage of the synthesis. For example quinolin-2-one (**1a**) in method B can be halogenated using N-chlorosuccinimide in a suitable solvent such as DMF at a suitable temperature such as room temperature to give the corresponding 6-chloro-quinolin-2-one (**1c**) wherein R³ is Cl.

5

Alternatively intermediates (**19 a-b**) wherein R³ is H in method C can be halogenated in the presence of N-chloro and N-bromosuccinimide in a suitable solvent such as DMF to give the corresponding 6-chloro and 6-bromoquinolin-2-ones (**20a-c**).

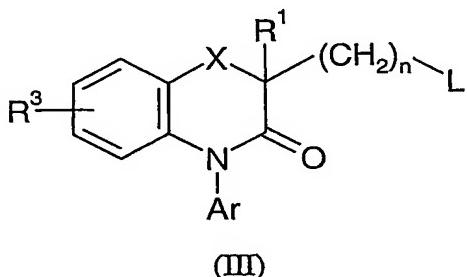
**20a-c**

- 10 It will be appreciated that methods A to D above relate to methods for the preparation of compounds of formula I wherein Ar is (i) and R^{2c} is hydrogen. Compounds of formula I wherein Ar is (i) and R^{2c} can be other than hydrogen, can be prepared using any of the general methods mentioned above, starting from the 15 corresponding N-arylated quinolin-2-one (**27**). A general method for preparing said intermediates is illustrated in Scheme 5. Commercially available 3-(2-Bromo-phenyl)-propionic acids (**25**) can be converted to amide (**26**) using standard amide coupling conditions and converted to the N-arylated quinolin-2-ones (**27**) by an intramolecular, palladium catalysed cyclisation according to the method of 20 Buchwald et al (Tetrahedron, 1996, 52, p. 7525).



Scheme 5

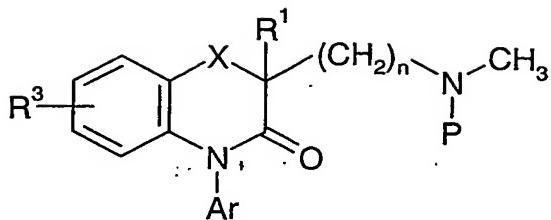
The present invention provides a process for the preparation of a compound of formula (I) comprising reacting methylamine with a compound of formula



wherein R¹, R³, X, n and Ar have the values defined for formula I above and L is a suitable leaving group such as for example chloride, bromide, iodide or mesylate.

The reaction can be carried out as described above, by reacting a compound of formula (III) with methylamine for example in the form of aqueous methylamine, optionally in the presence of a catalytic amount of a suitable iodide, such as potassium iodide (KI), in ethanol at 100°C provided the racemic amine products (6) and (7) respectively, in moderate yields.

15 The present invention provides a further process for the preparation of a compound of formula (I) comprising the N-deprotection of a compound of formula



(IV)

wherein R¹, R³, X, n and Ar have the values defined for formula I above and P is a suitable nitrogen protecting group such as those described in Greene, for example a

- 5 Boc group. The reaction is carried out using suitable deprotecting conditions such as those described in Greene according to the nature of the nitrogen-protecting group used (P). For example, for compounds protected with a Boc group they can be deprotected in the presence of trifluoroacetic acid (TFA) in a suitable organic solvent such as dichloromethane (DCM).

10 Compounds of the present invention are norepinephrine reuptake inhibitors and are selective over other neurotransmitters, such as dopamine or serotonin, that is their binding affinity at the norepinephrine transporter is higher than their affinity for other transporters or other receptors. In addition, they are acid stable.

Thus, the present invention provides a compound of formula (I), formula
15 (Ia) or formula (II), or a pharmaceutically acceptable salt thereof, for use in therapy; and a compound of formula (I), formula (Ia) or formula (II), or a pharmaceutically acceptable salt thereof, for use as a selective inhibitor of the reuptake of norepinephrine

Further, the present invention also provides a compound of formula (I),
20 formula (Ia) or formula (II), or a pharmaceutically acceptable salt thereof, for selectively inhibiting the reuptake of norepinephrine; and a compound of formula (I), formula (Ia) or formula (II), or a pharmaceutically acceptable salt thereof, for treating disorders associated with norepinephrine dysfunction in mammals; and the use of a compound of formula (I), formula (Ia) or formula (II), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for selectively inhibiting the reuptake of norepinephrine; and the use of a compound of formula (I), formula (Ia) or formula (II), or a pharmaceutically acceptable salt thereof, in the

manufacture of a medicament for the treatment of disorders associated with norepinephrine dysfunction in mammals, including the disorders listed herein.

Further, the present invention provides a method for selectively inhibiting the reuptake of norepinephrine in mammals, comprising administering to a patient in need thereof an effective amount of a compound of formula (I), formula (Ia) or formula (II), or a pharmaceutically acceptable salt thereof; and a method for treating disorders associated with norepinephrine dysfunction in mammals, comprising administering to a patient in need thereof an effective amount of a compound of formula (I), formula (Ia) or formula (II), or a pharmaceutically acceptable salt thereof.

Disorders associated with norepinephrine dysfunction in mammals, mentioned above in either the uses or the methods of the present invention, include, for example, nervous system conditions such as those selected from the group consisting of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder (ADD) due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, mania, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, TIC disorders, cognitive disorders including mild cognitive impairment (MCI), dementia of the Alzheimers type (DAT), vascular dementia and cognitive impairment associated with schizophrenia (CIAS), hypotensive states including orthostatic hypotension, and pain including chronic pain, neuropathic pain and antinociceptive pain.

In addition to the compounds of formula (I), formula (Ia) and formula (II), and processes for the preparation of said compounds, the present invention further

provides pharmaceutical compositions comprising a compound of formula (I), formula (Ia) or formula (II), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The compounds of the present invention may be used as medicaments in
5 human or veterinary medicine. The compounds may be administered by various routes, for example, by oral or rectal routes, topically or parenterally, for example by injection, and are usually employed in the form of a pharmaceutical composition.

Such compositions may be prepared by methods well known in the pharmaceutical art and normally comprise at least one active compound in
10 association with a pharmaceutically acceptable diluent or carrier. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier or diluted by a carrier, and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container. Where the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts
15 as a vehicle, excipient or medium for the active ingredient. Thus, the composition may be in the form of tablets, lozenges, sachets, cachets, elixirs, suspensions, solutions, syrups, aerosol (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, injection solutions and suspensions and sterile packaged
20 powders.

Some examples of suitable carriers are lactose, dextrose, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates such as starch and petroleum jelly, sucrose sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup,
25 methyl cellulose, methyl- and propyl- hydrobenzoate, talc, magnesium stearate and mineral oil. The compounds of formula (I) can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations. The preparations indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents,
30 emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants, flavourings and/or one or more further active compounds, e.g. one or more vitamins. Compositions of the invention may be formulated so as to provide, quick,

sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg, more usually about 25 to about 5 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary doses for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

10 The following examples illustrate particular embodiments of compounds of the present invention and methods for their preparation.

Method A

Preparation of Intermediates

1-Phenyl-3,4-dihydro-1*H*-quinolin-2-one (2a)

A stirred mixture of 3,4-Dihydro-1*H*-quinolin-2-one (**1a**) (1.47 g, 10 mmol), K₂CO₃ (2.9 g, 21 mmol), *trans*-cyclohexane-1,2-diamine (240 µL, 2 mmol) and 20 bromobenzene (3.16 mL, 30 mmol) in 1,4-dioxane (10 mL) was heated under a nitrogen atmosphere at 125°C for 5 min to deoxygenate the reaction mixture. Copper (I) iodide (380 mg, 2 mmol) was added in one portion and the reaction mixture was refluxed overnight at 125°C. After cooling to rt, the reaction mixture was poured into ethyl acetate (100 mL) and extracted with water. The organic layer 25 was separated, dried over MgSO₄ and concentrated. Treatment of the residue with ether (100 mL) and cooling (ice bath) gave the product as a white solid after filtration (1.77 g, 79%).

6-Fluoro-1-*p*-tolyl-3,4-dihydro-1*H*-quinolin-2-one (2b)

30 This was prepared using the method described for (**2a**) using 6-Fluoro-3,4-dihydro-1*H*-quinolin-2-one (**1b**) (617 mg, 3.7 mmol) and 4-bromotoluene (1.91 g, 11 mmol) to give the crude product, which was purified using automated chromatography

(silica) (0 to 60% ethyl acetate\cyclohexane gradient) to provide the product as a light brown solid (880 mg, 92%).

3-Methyl-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (3a)

5 To a soln of (2a) (892 mg, 4 mmol) in anhydrous THF (40 mL) at -78°C under nitrogen was added LiHMDS (4.4 mL, 1M soln in hexanes, 4.4 mmol) dropwise over 10 min. The reaction mixture was left at -78°C for 30 min and then a solution of methyl iodide (298 µL, 4.8 mmol) in THF (1 mL) was added dropwise. The reaction mixture was warmed slowly to rt, quenched with water (2 mL) and extracted with ethyl acetate (100 mL). The organic layer was separated, dried over 10 MgSO₄ and concentrated. The residue was purified by column chromatography (silica, gradient 100% hexane to ethyl acetate\hexane 3:10) giving the product as an oil (667 mg, 70%).

15 **3-Ethyl-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (3b)**

This was prepared in a similar manner to (3a) on a 1.5 mmol scale using 1-iodoethane (125 µL, 1.1 eq.) as the alkylating agent. The crude product (378 mg) was used directly in the next step.

20 **3-(3-Chloro-propyl)-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (4a)**

To a soln of (2a) (892 mg, 4 mmol) in anhydrous THF (40 mL) at -78°C under nitrogen was added LiHMDS (4.4 mL, 1M soln in hexanes, 4.4 mmol) dropwise over 10 min. The reaction mixture was left at -78°C for 30 min and then a solution of 1-bromo-3-chloropropane (405 µL, 4.4 mmol) in THF (1 mL) was added 25 dropwise. The reaction mixture was warmed slowly to rt, quenched with water (2 mL) and extracted with ethyl acetate (100 mL). The organic layer was separated, dried over MgSO₄ and concentrated. The crude product (1.2 g) was used directly in the next step.

30 **3-(3-Chloro-propyl)-6-fluoro-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (4b)**

This was prepared from (2b) (300 mg, 1.17 mmol) using the method described for (4a) using 1-bromo-3-chloropropane (140 µL, 1.4 mmol) as the alkylating agent. The crude product (399 mg) was used directly in the next step.

**3-(2-Chloro-ethyl)-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (4c)**

This was prepared from (2a) (892 mg, 4.0 mmol) using the method described for (4a) using 1-bromo-2-chloroethane (365 μ L, 4.4 mmol) as the alkylating agent.

5 The crude product (1 g) was used directly in the next step.

3-(3-Chloro-propyl)-3-methyl-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (5a)

This was prepared from (3a) (462 mg, 1.95 mmol) using the method described for (4a) using 1-bromo-3-chloropropene (270 μ L, 2.7 mmol) as the alkylating agent.

10 The crude product (650 mg) was used directly in the next step.

3-(3-Chloro-propyl)-3-ethyl-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (5b)

This was prepared from (3b) (378 mg, 1.5 mmol) using the method described for (4a) using 1-bromo-3-chloropropene (179 μ L, 1.8 mmol) as the alkylating agent.

15 The crude product (528 mg) was used directly in the next step.

Examples**Example 1: 3-(3-Methylamino-propyl)-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (6a)**

20 A soln of (4a) (1.2 g, 4 mmol), potassium iodide (200 mg, 1.2 mmol) and aqueous 40% methylamine (12 mL) in ethanol (30 mL) was refluxed at 100°C under nitrogen for 3 h. The reaction mixture was cooled, poured into water and extracted with ethyl acetate (100 mL). The organic layer was separated, dried over $MgSO_4$ and 25 concentrated. The product was purified by preparative LCMS to give 500 mg of the racemate. The racemate was separated into its individual enantiomers using chiral HPLC. 1H NMR (300 MHz, $CDCl_3$) (racemate & isomer) δ 1.5-1.73 (m, 4H), 1.88-1.97 (m, 1H), 2.43 (s, 3H), 2.62 (t, J = 6.69 Hz, 2H), 2.70-2.79 (m, 1H), 2.84-2.92 (m, 1H), 3.15 (dd, J = 15.45, 5.28 Hz, 1H), 6.33 (d, J = 7.73 Hz, 1H), 6.95-7.06 (m, 2H), 7.19-7.22 (m, 3H), 7.38-7.43 (m, 1H), 7.47-7.52 (m, 2H). LCMS (12 minute method) $[M+H]^+$ = 295 @ Rt 4.0 min (100%).

Example 2: 6-Fluoro-3-(3-methylamino-propyl)-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (6b)

This was prepared in an identical manner to (6a) using crude (4b) (399 mg) to give the crude product, which was purified by preparative LCMS to give the product (35
5 mg). ^1H NMR (300 MHz, CDCl_3) (racemate) δ 1.40-1.70 (m, 3H), 1.75-1.90 (m,
4H), 2.34 (s, 3H), 2.36 (s, 3H), 2.50-2.83 (m, 2H), 3.01-3.08 (m, 1H), 6.21-6.26 (m,
1H), 6.62-6.68 (m, 1H), 6.82-6.86 (m, 1H), 6.99 (d, $J= 8.1$ Hz, 2H), 7.22 (d, $J= 8.1$
Hz, 2H). LCMS (12 minute method) $[\text{M}+\text{H}]^+ = 327$ @ Rt 4.8 min (100%).

10 **Example 3: 3-(2-Methylamino-ethyl)-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (6c)**

This was prepared in an identical manner to (6a) using crude (4c) (1g) to give the racemate (80 mg). The racemate was separated into its individual enantiomers using chiral HPLC. ^1H NMR (300 MHz, CDCl_3) (racemate & isomer) δ ppm 1.64-1.76
15 (m, 1H), 1.79 (br, 1H), 2.03-2.18 (m, 1H), 2.44 (s, 3H), 2.71-2.82 (m, 2H), 2.82-
2.94 (m, 2H), 3.09-3.21 (m, 1H), 6.33 (dd, $J= 7.91, 1.32$ Hz, 1H), 6.94-7.07 (m,
2H), 7.18-7.24 (m, 3H), 7.37-7.44 (m, 1H), 7.47-7.54 (m, 2H). LCMS (12 minute
method) $[\text{M}+\text{H}]^+ = 281$ @Rt 3.82 min (100%).

20 **Example 4: 3-Methyl-3-(3-methylamino-propyl)-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (7a)**

This was prepared in an identical manner to (6a) using crude (5a) (650 mg) to give the crude product (198 mg), which was purified by preparative LCMS. The purified racemate was then separated into its individual enantiomers using chiral HPLC. ^1H
25 NMR (300 MHz, CDCl_3) (isomer) δ ppm 1.27 (s, 3H), 1.43 (br, 1H), 1.53-1.66 (m,
4H), 2.39 (s, 3H), 2.54 (t, $J= 6.12$ Hz, 2H), 2.91 (d, $J= 15.64$ Hz, 1H), 2.98 (d, $J=$
15.64 Hz, 1H), 6.28 (dd, $J= 7.91, 1.32$ Hz, 1H), 6.97 (td, $J= 7.21, 1.41$ Hz, 1H),
7.03 (td, $J= 7.68, 1.98$ Hz, 1H), 7.14-7.22 (m, 3H), 7.36-7.44 (m, 1H), 7.46-7.53 (m,
2H). LCMS (12 minute method) $[\text{M}+\text{H}]^+ = 309$ @Rt 4.21 min (100%).

30

Example 5: 3-Ethyl-3-(3-methylamino-propyl)-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (7b)

This was prepared in an identical manner to (6a) using crude (5b) (528 mg) to give the crude product (105 mg), which was purified by preparative LCMS. The purified racemate was then separated into its individual enantiomers using chiral HPLC.

¹H NMR (300 MHz, CDCl₃) (racemate) δ 0.93 (t, J= 7.53 Hz, 3H), 1.56-1.75 (m, 6H), 1.91 (bs, 1H), 2.41 (s, 3H), 2.55-2.60 (m, 2H), 2.91 (d, J= 15.82, 1H), 3.02 (d, J= 15.82, 1H), 6.25-6.28 (m, 1H), 6.94-7.05 (m, 2H), 7.16-7.19 (m, 3H), 7.38-7.43 (m, 1H), 7.4-7.52 (m, 2H). ¹H NMR (300 MHz, MeOD-d4) (isomer D-tartrate salt) δ 0.85 (t, J= 7.53 Hz, 3H), 1.45-1.75 (m, 6H), 2.57 (s, 2H), 2.83-2.89 (m, 2H), 3.01-3.06 (d, J= 16.01, 1H), 4.32 (s, 2H), 6.11-6.14 (m, 1H), 6.89-6.97 (m, 2H), 7.09 (d, J= 7.16 Hz, 2H), 7.15-7.18 (m, 1H), 7.37 (t, J= 7.35 Hz, 1H), 7.46 (t, J= 7.35 Hz, 2H). LCMS (12 minute method) [M+H]⁺ = 323 @ Rt 4.9 min (98%).

Method B

15 Preparation of Intermediates

1-p-Tolyl-3,4-dihydro-1*H*-quinolin-2-one (2c)

A stirred mixture of 3,4-Dihydro-1*H*-quinolin-2-one (1a) (4.41 g, 30 mmol), K₂CO₃ (8.7 g, 63 mmol), *trans*-cyclohexane-1,2-diamine (720 μL, 2 mmol) and 4-bromotoluene (15.4 g, 90 mmol) in 1,4-dioxane (30 mL) was heated under a nitrogen atmosphere at 125°C for 5 min to deoxygenate the reaction mixture. Copper (I) iodide (1.14 g, 2 mmol) was added in one portion and the reaction mixture was refluxed overnight at 125°C. After cooling to rt, the reaction mixture was filtered through celite, poured into ethyl acetate (100 mL) and extracted with water. The organic layer was separated, dried over MgSO₄ and concentrated. Treatment of the residue with ether (200 mL) and cooling (ice bath) gave the product as a white solid after filtration (6.2 g, 87%).

1-Phenyl-3-propyl-3,4-dihydro-1*H*-quinolin-2-one (3c)

This was prepared from (2a) (669 mg, 3 mmol) and 1-iodopropane (352 μl, 1.2 eq.) as the alkylating agent. The crude product (780 mg) was used directly in the next step.

3-Ethyl-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (3d)

This was prepared from (2c) (711 mg, 3 mmol) and 1-iodoethane (265 μ l, 1.2 eq.) as the alkylating agent. The crude product (800 mg) was used directly in the next
5 step.

3-Propyl-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (3e)

This was prepared from (2c) (711 mg, 3 mmol) and 1-iodopropane (352 μ l, 1.2 eq.) as the alkylating agent. The crude product (840 mg) was used directly in the next
10 step.

3-Butyl-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (3f)

This was prepared from (2c) (711 mg, 3 mmol) and 1-iodobutane (354 μ l, 1.1 eq.) as the alkylating agent. The crude product (790 mg) was used directly in the next
15 step.

3-Isopropyl-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (3g)

This was prepared from (2c) (711 mg, 3 mmol) and 2-iodopropane (330 μ l, 1.1 eq.) as the alkylating agent. The crude product (806 mg) was used directly in the next
20 step.

3-Allyl-3-ethyl-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (11b)

To a soln of (3d) (800 mg, 2.7 mmol) in anhydrous THF (30 mL) at -78°C under nitrogen was added LiHMDS (3 mL, 1M soln in hexanes, 3 mmol) dropwise over
25 10 min. The reaction mixture was left at -78°C for 30 min and then a solution of allyl bromide (280 μ L, 3.2 mmol) in THF (1 mL) was added dropwise. The reaction mixture was warmed slowly to rt, quenched with water (2 mL) and extracted with ethyl acetate (100 mL). The organic layer was separated, dried over MgSO₄ and concentrated. The crude product (920 mg) was used directly in the next step.

30

3-Ethyl-3-(3-hydroxypropyl)-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (12b)



To a soln of (11b) (732 mg, 2.4 mmol) in anhydrous THF (25 mL) at 0°C under nitrogen was added 9-BBN (12 mL, 0.5M soln in THF, 6 mmol, 2.5 eq.) dropwise over 10 min. The reaction mixture was warmed to rt and left to stir overnight. The resultant yellow soln was cooled to 0°C and then quenched carefully with ethanol (3 mL), followed by aq. NaOH (1.8 mL, 3N soln). Finally, aq. H₂O₂ (1.8 mL, 37% soln) was added dropwise maintaining the internal reaction mixture temp between 5 and 10 °C. The reaction mixture was warmed to rt and then refluxed for 90 min. The reaction mixture was cooled to rt, poured into ethyl acetate and water and extracted. The organic layer was separated, dried over MgSO₄ and concentrated. The crude product was purified using automated chromatography (silica) (0 to 60% ethyl acetate\cyclohexane gradient) to provide (12b) as a clear oil (540 mg, 70%).

Examples

15 **Example 6: 3-Ethyl-3-(3-methylamino-propyl)-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (13b)**

To a soln of (12b) (540 mg, 1.67 mmol) and triethylamine (350 μL, 2.5 mmol) in anhydrous THF (20 mL) at 0°C under nitrogen was added dropwise a soln of methanesulfonyl chloride (142 μL, 1.8 mmol) in THF (1 mL). The reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was poured into ethyl acetate and water and extracted. The organic layer was separated, dried over MgSO₄ and concentrated. The crude mesylate (670 mg, 100%) was dissolved in ethanol (10 mL) and aqueous 40% methylamine (5 mL) and heated at 65°C under nitrogen for 2 h. The reaction mixture was cooled, poured into water and extracted with ethyl acetate (100 mL). The organic layer was separated, dried over MgSO₄ and concentrated. The product was purified by SCX-2 to give 384 mg of the racemate. The racemate was separated into its individual enantiomers using chiral HPLC. Each enantiomer was dissolved in CH₂Cl₂ (2 mL) and treated with 1 equivalent of D-tartaric acid dissolved in a minimum volume of warm methanol. The resultant soln was concentrated and the solid was dried under vacuo to provide the D-tartrate salt of the amine. ¹H NMR (300 MHz, CDCl₃) (racemate) δ 0.92 (t, J= 7.44 Hz, 3H), 1.49-1.75 (m, 6H), 1.81 (br, 1H), 2.40 (s, 6H), 2.57 (t, J= 6.59 Hz, 2H), 2.89

(d, $J = 15.82$ Hz, 1H), 3.00 (d, $J = 15.82$ Hz, 1H), 6.29 (d, $J = 7.91$ Hz, 1H), 6.92-7.08 (m, 4H), 7.16 (d, $J = 7.16$ Hz, 1H), 7.29 (d, $J = 7.91$ Hz, 2H). ^1H NMR (300 MHz, MeOD-d4) (isomer D-tartrate salt) δ 0.93 (t, $J = 7.44$ Hz, 3H), 1.54-1.84 (m, 6H), 2.42 (s, 3H), 2.66 (s, 3H), 2.91-3.00 (m, 3H), 3.11 (d, $J = 15.83$ Hz, 1H), 4.41 (s, 2H), 6.22-6.27 (m, 1H), 6.80-7.07 (m, 4H), 7.21-7.27 (m, 1H), 7.36 (d, $J = 7.91$ Hz, 2H). LCMS (12 minute method) $[\text{M}+\text{H}]^+ = 337$ @Rt 5.21 min (100%).

5 Example 7: 3-(3-Methylamino-propyl)-1-phenyl-3-propyl-3,4-dihydro-1*H*-quinolin-2-one (13a)

10 This was prepared from (3c) (780 mg, 2.9 mmol) using the same synthetic sequence described in method B (3d to 13b) to give 233 mg of the racemate. The racemate was separated into its individual enantiomers using chiral HPLC and each enantiomer was converted into its D-tartrate salt as described for (13b). ^1H NMR (300 MHz, CDCl₃) (racemate) δ 0.88 (t, $J = 7.16$ Hz, 3H), 1.26-1.48 (m, 2H), 1.50-1.78 (m, 7H), 2.40 (s, 3H), 2.56 (t, $J = 6.59$ Hz, 2H), 2.92 (d, $J = 15.83$ Hz, 1H), 3.01 (d, $J = 15.83$ Hz, 1H), 6.25-6.28 (m, 1H), 6.94-7.05 (m, 2H), 7.16-7.19 (m, 3H), 7.37-7.42 (m, 1H), 7.47-7.52 (m, 2H). ^1H NMR (300 MHz, MeOD-d4) (isomer D-tartrate salt) δ 0.77-0.82 (t, $J = 7.06$ Hz, 3H), 1.24-1.35 (m, 2H), 1.44-1.51 (m, 2H), 1.69 (bs, 3H), 2.56 (s, 3H), 2.84-2.89 (m, 3H), 3.01-3.06 (d, $J = 15.83$ Hz, 1H), 3.20-3.22 (q, $J=1.55$ Hz, 2H), 4.30 (s, 2H), 6.11-6.14 (dd, $J = 7.72, 2.26$ Hz, 1H), 6.89-6.97 (m, 2H), 7.07-7.10 (m, 2H), 7.14-7.17 (m, 1H), 7.34-7.39 (t, $J = 7.35$ Hz, 1H), 7.43-7.48 (t, $J = 7.35$ Hz, 2H). LCMS (12 minute method) $[\text{M}+\text{H}]^+ = 337$ @ Rt 5.2 min (100%).

25 Example 8: 3-(3-Methylamino-propyl)-3-propyl-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (13c)

This was prepared from (3e) (840 mg, 2.6 mmol) using the same synthetic sequence described in method B (3d to 13b) to give 393 mg of the racemate. The racemate was separated into its individual enantiomers using chiral HPLC and each enantiomer was converted into its D-tartrate salt as described for (13b). ^1H NMR (300 MHz, CDCl₃) (racemate) δ 0.88 (t, $J = 7.16$ Hz, 3H), 1.20-1.75 (m, 11H), 2.39 (s, 3H), 2.40 (s, 3H), 2.90 (d, $J = 15.64$ Hz, 1H), 2.99 (d, $J = 15.64$ Hz, 1H), 6.29 (d,

J= 7.72 Hz, 1H), 6.93-7.07 (m, 4H), 7.14-7.16 (m, 1H), 7.25-7.31 (m, 2H). ^1H NMR (300 MHz, MeOD-d4) (isomer D-tartrate salt) δ 0.91 (t, J= 7.06 Hz, 3H), 1.28-1.85 (m, 8H), 2.44 (s, 3H), 2.68 (s, 3H), 2.94-2.99 (m, 3H), 3.14 (d, J= 15.82 Hz, 1H), 4.41 (s, 2H), 6.25-6.28 (m, 1H), 7.02-7.07 (m, 4H), 7.25-7.28 (m, 1H), 7.38 (d, J= 7.91 Hz, 2H). LCMS (12 minute method) $[\text{M}+\text{H}]^+$ = 351 @ Rt 5.6 min (100%).

Example 9: 3-Butyl-3-(3-methylamino-propyl)-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (13d)

This was prepared from (3f) (790 mg, 2.7 mmol) using the same synthetic sequence described in method B (3d to 13b) to give 334 mg of the racemate. The racemate was separated into its individual enantiomers using chiral HPLC and each enantiomer was converted into its D-tartrate salt as described for (13b). ^1H NMR (300 MHz, CDCl_3) (racemate) δ 0.87 (t, J= 6.97 Hz, 3H), 1.20-1.40 (m, 4H), 1.55-1.74 (m, 6H), 2.40 (s, 3H), 2.40 (s, 3H), 2.55 (t, J= 6.78 Hz, 3H), 2.91 (d, J= 15.63 Hz, 1H), 2.99 (d, J= 15.63 Hz, 1H), 6.28-6.31 (m, 1H), 6.93-7.00 (m, 2H), 7.02-7.06 (m, 2H), 7.14-7.16 (m, 1H), 7.29 (d, J= 8.07 Hz, 2H). ^1H NMR (300 MHz, MeOD-d4) (isomer D-tartrate salt) δ 0.90 (t, J= 6.97 Hz, 3H), 1.20-1.85 (m, 10H), 2.44 (s, 3H), 2.68 (s, 3H), 2.94-2.99 (m, 3H), 3.14 (d, J= 15.82 Hz, 1H), 4.42 (s, 2H), 6.25-6.28 (m, 1H), 7.00-7.07 (m, 4H), 7.25-7.28 (m, 1H), 7.38 (d, J= 7.91 Hz, 2H). LCMS (12 minute method) $[\text{M}+\text{H}]^+$ = 365 @ Rt 5.9 min (100%).

Example 10: 3-Isopropyl-3-(3-methylamino-propyl)-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (13e)

This was prepared from (3g) (806 mg, 2.89 mmol) using the same synthetic sequence described in method B (3d to 13b) to give 307 mg of the racemate. ^1H NMR (300 MHz, CDCl_3) (racemate) δ ppm 0.92 (dd, J= 8.95, 6.88 Hz, 6H), 1.39-1.88 (m, 5H), 2.12-2.23 (m, 1H), 2.39 (s, 3H), 2.40 (s, 3H), 2.56 (t, J= 6.78 Hz, 2H), 2.94 (d, J= 15.92 Hz, 1H), 3.00 (d, J= 15.92 Hz, 1H), 6.28 (dd, J= 7.82, 1.04 Hz, 1H), 6.92-7.06 (m, 4H), 7.16 (dd, J= 6.97, 1.13 Hz, 1H), 7.29 (d, J= 7.91 Hz, 2H). LCMS (12 minute method) $[\text{M}+\text{H}]^+$ = 351 @Rt 5.55 min (100%).

Example 11: 6-Chloro-3-ethyl-3-(3-methylamino-propyl)-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (13f)

This was prepared from (1c) using the same synthetic sequence described in method B to give 205 mg of the racemate. The racemate was separated into its individual
5 enantiomers using chiral HPLC and each enantiomer was converted into its D-tartrate salt as described for (13b). ^1H NMR (300 MHz, CDCl_3) (racemate) δ ppm 0.91 (t, $J= 7.44$ Hz, 3H), 1.50-1.75 (m, 6H), 2.15 (br, 1H), 2.40 (s, 3H), 2.41 (s, 3H), 2.55-2.64 (m, 2H), 2.85 (d, $J= 16.01$ Hz, 1H), 2.97 (d, $J= 16.01$ Hz, 1H), 6.23 (d, $J= 8.85$ Hz, 1H), 6.97 (dd, $J= 8.67, 2.45$ Hz, 1H), 7.02 (d, $J= 8.29$ Hz, 2H), 7.14 (d, $J= 2.26$ Hz, 1H), 7.29 (d, $J= 8.10$ Hz, 2H). ^1H NMR (300 MHz, MeOD-d_4) (isomer, D-tartrate salt) δ ppm 0.84 (t, $J= 7.35$ Hz, 3H), 1.40-1.75 (m, 6H), 2.32 (s, 3H), 2.57 (s, 3H), 2.80-2.92 (m, 3H), 3.01 (d, $J= 16.20$ Hz, 1H), 4.31 (s, 2H), 6.13 (d, $J= 8.67$ Hz, 1H), 6.92-6.98 (m, 3H), 7.19 (d, $J= 2.26$ Hz, 1H), 7.26 (d, $J= 7.91$ Hz, 2H). LCMS (12 minute method) $[\text{M}+\text{H}]^+ = 371/373 @ \text{Rt } 5.75 \text{ min (100%).}$

15

Example 12: 6-Chloro-1-(4-chloro-phenyl)-3-ethyl-3-(3-methylamino-propyl)-3,4-dihydro-1*H*-quinolin-2-one (13g)

This was prepared from (1c) using the same synthetic sequence described in method B to give 222 mg of the racemate, which was purified by preparative LCMS. ^1H NMR (300 MHz, CDCl_3) (racemate) δ ppm 0.84 (t, $J= 7.44$ Hz, 3H), 1.40-1.70 (m, 6H), 2.35 (br, 4H), 2.49-2.56 (m, 2H), 2.80 (d, $J= 16.01$ Hz, 1H), 2.90 (d, $J= 16.01$ Hz, 1H), 6.14 (d, $J= 8.67$ Hz, 1H), 6.93 (dd, $J= 8.67, 2.26$ Hz, 1H), 7.04 (ddd, $J= 9.04, 2.83, 2.45$ Hz, 2H), 7.09 (d, $J= 2.26$ Hz, 1H), 7.36-7.43 (m, 2H). LCMS (12 minute method) $[\text{M}+\text{H}]^+ = 391/393 @ \text{Rt } 5.67 \text{ min (92%).}$

Method C

30 **Preparation of intermediates**

1-(4-Methoxy-benzyl)-3,4-dihydro-1*H*-quinolin-2-one (14)

A 5 litre flange-neck flask equipped with an air stirrer and paddle, thermometer, nitrogen bubbler and pressure equalising dropping funnel was charged with sodium hydride (25.5g, 60% oil dispersion, 0.637 mol) and 40-60 pet. ether (100 ml). The mixture was stirred briefly and then allowed to settle under nitrogen. After 5 decanting the supernatant liquid, the vessel was charged with dimethylformamide (2 litres). The well stirred suspension was cooled to 7-8°C using an external ice-bath. Then a soln of 3,4-dihydro-1*H*-quinolin-2-one (**1a**) (73.6g, 0.5 mole) in anhydrous dimethylformamide (500 ml) was added dropwise over 25 min. The mixture was stirred at 7-8°C for 30 min. then 4-methoxybenzyl chloride (102 g, 0.65 mole, 1.3 10 eq.) was added over 10 min. The reaction mixture was left to stir for 2 h. at <10°C then allowed to warm-up to room temperature and stirred overnight. The stirred reaction mixture was quenched with ice/water (2.5 litres) and cooled to 15 °C using an external ice-bath. The white solid was isolated by filtration and washed with water. After drying in vacuo at 40°C overnight the product was obtained (113.4g, 15 85%).

1-(4-Methoxy-benzyl)-3-methyl-3,4-dihydro-1*H*-quinolin-2-one (**15**)

To a soln of (**14**) (20 g, 75 mmol) in anhydrous THF (400 mL) at -78°C under nitrogen was added LiHMDS (78.6 mL, 1M soln in hexanes, 78.6 mmol) dropwise 20 over 10 min. The reaction mixture was left at -78°C for 30 min and then a solution of methyl iodide (5.13 mL, 83 mmol) in THF (5 mL) was added dropwise. The reaction mixture was warmed slowly to rt, quenched with water (50 mL) and extracted with ethyl acetate (400 mL). The organic layer was separated, dried over MgSO₄ and concentrated to give the product as a yellow solid (21 g, 100%) that was 25 used directly in the next step.

3-Allyl-1-(4-methoxy-benzyl)-3-methyl-3,4-dihydro-1*H*-quinolin-2-one (**16b**)

To a soln of (**15**) (20.5 g, 73 mmol) in anhydrous THF (400 mL) at -78°C under nitrogen was added LiHMDS (80 mL, 1M soln in hexanes, 80 mmol) dropwise over 30 10 min. The reaction mixture was left at -78°C for 30 min and then a solution of

allyl bromide (7.6 mL, 87 mmol) in THF (5 mL) was added dropwise. The reaction mixture was warmed slowly to rt, quenched with water (100 mL) and extracted with ethyl acetate (400 mL). The organic layer was separated, dried over MgSO₄ and concentrated to give the product as an orange oil (23.9 g, 100%) that was used
5 directly in the next step.

3-(3-Hydroxy-propyl)-1-(4-methoxy-benzyl)-3-methyl-3,4,4a,8a-tetrahydro-1*H*-quinolin-2-one (17b)

To a soln of (16b) (23.9 g, 74 mmol) in anhydrous THF (400 mL) at 0°C under
10 nitrogen was added 9-BBN (370 mL, 0.5M soln in THF, 185 mmol, 2.5 eq.) dropwise over 10 min. The reaction mixture was warmed to rt and left to stir overnight. The resultant yellow soln was cooled to 0°C and then quenched carefully with ethanol (95 mL), followed by aq. NaOH (60 mL, 3N soln). Finally, aq. H₂O₂ (60 mL, 37% soln) was added dropwise maintaining the internal reaction mixture
15 temp between 5 and 10 °C. The reaction mixture was warmed to rt and then refluxed for 90 min. The reaction mixture was cooled to rt, poured into ethyl acetate and water and extracted. The organic layer was separated, dried over MgSO₄ and concentrated. The crude product was purified using automated chromatography (silica) (0 to 80% ethyl acetate\cyclohexane gradient) to provide the product as a
20 clear oil (21.3 g, 84%).

1-(4-Methoxy-benzyl)-3-methyl-3-(3-methylamino-propyl)-3,4,4a,8a-tetrahydro-1*H*-quinolin-2-one (18b)

To a soln of (17b) (18 g, 53 mmol) and triethylamine (11.1 mL, 79 mmol) in
25 anhydrous THF (450 mL) at 0°C under nitrogen was added dropwise a soln of methanesulfonyl chloride (4.52 mL, 58 mmol) in THF (50 mL). The reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was poured into ethyl acetate and water and extracted. The organic layer was separated, dried over MgSO₄ and concentrated. The crude mesylate (22 g, 99%) was dissolved in ethanol
30 (500 mL) and aqueous 40% methylamine (200 mL) and heated at 65°C under nitrogen for 2 h. The reaction mixture was cooled, concentrated and then extracted

with ethyl acetate (300 mL). The organic layer was washed with water, brine, dried over MgSO₄ and concentrated to give the crude product (17.8 g, 96%).

Methyl-[3-(3-methyl-2-oxo-1,2,3,4,4a,8a-hexahydro-quinolin-3-yl)-propyl]-

5 carbamic acid *tert*-butyl ester (19b)

A mixture of (18b) (17.8 g, 50.5 mmol) and anisole (5.5 mL, 50.5 mmol) in trifluoroacetic acid (250 mL) was heated at 65°C under nitrogen for 2 h. The reaction mixture was concentrated under vacuo and the residue was dissolved in methanol (10 mL). The methanol soln was applied to an SCX-2 column (300 g, pre-washed with methanol) and the column washed with methanol (approx 1 litre) until the soln became colourless. The product was eluted with 2N NH₃ in methanol (500 mL) and the basic soln was concentrated to provide 3-Methyl-3-(3-methylamino-propyl)-3,4-dihydro-1H-quinolin-2-one (9 g, 77%). To a soln of this amine (8.6 g, 37 mmol) in anhydrous THF (350 mL) at 0°C was added a soln of di-*tert*-butyl dicarbonate (8.34 g, 97%, 50.5 mmol) in THF (20 mL) dropwise. The reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was poured into ethyl acetate (400 mL) and water (200 mL) and extracted. The organic layer was separated, dried over MgSO₄ and concentrated to give the product as a yellow solid (12.26 g, 100%). This material was used without further purification.

20

Methyl-[3-(2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-propyl]-carbamic acid *tert*-butyl ester (19a)

This was prepared from (14) using the same synthetic sequence described in method C.

25

[3-(6-Chloro-1,2,3,4-tetrahydro-quinolin-3-yl)-propyl]-methyl-carbamic acid *tert*-butyl ester (20a)

To a soln of (19a) (2.75 g, 8.6 mmol) in anhydrous DMF (25 mL) at 0°C was added dropwise a soln of N-chlorosuccinimide (1.17 g, 8.7 mmol) in anhydrous DMF (3 mL). The reaction mixture was warmed to rt, stirred overnight and then poured into ethyl acetate (100 mL) and water (50 mL) and extracted. The organic layer was

separated, dried over MgSO₄ and concentrated to provide the product as a yellow oil (3 g, 98%) that was used without further purification.

Examples

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Example 13: 3-(3-Methylamino-propyl)-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (21a)

A stirred mixture of (19a) (100 mg, 0.31 mmol), K₂CO₃ (92 mg, 0.66 mmol), *trans*-

cyclohexane-1,2-diamine (8 μ L, 0.06 mmol) and 4-bromotoluene (162 mg, 0.94

10 mmol) in 1,4-dioxane (0.5 mL) was heated under a nitrogen atmosphere at 125°C

for 5 min to deoxygenate the reaction mixture. Copper (I) iodide (12 mg, 0.06 mmol) was added in one portion and the reaction mixture was refluxed overnight at 125°C. After cooling to rt, the reaction mixture was poured into ethyl acetate (100

mL) and extracted with water. The organic layer was separated, dried over MgSO₄

15 and concentrated. The crude product was purified using automated chromatography (silica) (0 to 80% ethyl acetate:cyclohexane gradient) to provide the Boc protected

product (70 mg, 54%). To a soln of this material (70 mg, 0.17 mol) in DCM (2 mL),

was added trifluoroacetic acid (197 μ L, 2.55 mmol, 15 eq.). The reaction mixture

was left to stir at room temperature for 90 min, concentrated under vacuo poured

20 into ethyl acetate (50 mL) and aq. NaHCO₃ (20 mL) and extracted. The organic layer was separated, dried over MgSO₄, concentrated and the crude product was

purified by SCX-2 to provide the racemate (40 mg, 75%). The racemate was

separated into its individual enantiomers using chiral HPLC. ¹H NMR (300 MHz,

CDCl₃) (racemate) δ 1.49-1.77 (m, 3H), 1.86-1.96 (m, 1H), 2.34 (bs, 1H), 2.40 (s,

25 3H), 2.43 (s, 3H), 2.61-2.66 (t, J= 6.88 Hz, 2H), 2.68-2.78 (m, 1H), 2.83-2.90 (m,

1H), 3.09-3.17 (m, 1H), 6.36 (dd; J= 7.7 Hz, 1.0 Hz, 1H), 6.94-7.03 (m, 2H), 7.08

(d, J= 8.2 Hz, 2H), 7.13-7.17 (m, 1H), 7.29 (d, J= 8.1 Hz, 2H); ¹H NMR (300 MHz,

MeOD-d4) (isomer, D-tartrate salt) δ 1.64 (bs, 1H), 1.89 (bs, 3H), 2.41(s, 3H), 2.70

(s, 3H), 2.75-2.87 (m, 1H), 2.91-3.06 (m, 3H), 3.20 (dd, J= 5.9, 15.26 Hz, 1H), 4.45

30 (s, 2H), 6.32-6.35 (m, 1H), 7.00-7.12 (m, 4H), 7.28-7.30 (m, 1H), 7.37 (d, J= 8.1 Hz, 2H). LCMS (12 minute method) [M+H]⁺ = 309 @ Rt 4.7 min (100%).



Example 14: 6-Chloro-3-(3-methylamino-propyl)-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (21n)

This was prepared from (20a) (132 mg, 0.29 mmol) using the same methods described for (21a) to provide the racemate (86 mg). ^1H NMR (300 MHz, CDCl_3) (racemate & isomer) δ 1.50-1.57 (m, 1H), 1.62-1.90 (m, 3H), 2.34 (s, 3H), 2.41 (s, 3H), 2.63-2.82 (m, 5H), 3.00-3.07 (m, 1H), 6.22 (d, $J=8.6$ Hz, 1H), 6.92 (dd, $J=2.45, 8.66$ Hz, 1H), 6.99 (d, $J=8.1$ Hz, 2H), 7.11 (d, $J=2.25$ Hz, 1H), 7.23 (d, $J=8.1$ Hz, 2H). LCMS (12 minute method) $[\text{M}+\text{H}]^+ = 343/345$ @ Rt 5.2 min (96%).

10

Example 15: 1-(3-Fluorophenyl)-3-(3-methylamino-propyl)-3,4-dihydro-1*H*-quinolin-2-one (21b)

This was prepared from (19a) (200 mg, 0.63 mmol) using the same two-step procedure described for (21a) to provide the racemate (83 mg). ^1H NMR (300 MHz, CDCl_3) (racemate) δ 1.60-1.70 (m, 1H), 1.92 (br, 3H), 2.64 (bs, 3H), 2.72-2.74 (m, 1H), 2.86-3.09 (m, 4H), 6.35 (dd, $J=7.72, 1.510$ Hz, 1H), 6.94-7.23 (m, 6H), 7.43-7.51 (m, 1H). LCMS (12 minute method) $[\text{M}+\text{H}]^+ = 313$ @ Rt 4.4 min (100%).

20

Example 16: 1-(4-Chlorophenyl)-3-(3-methylamino-propyl)-3,4-dihydro-1*H*-quinolin-2-one (21c)

This was prepared from (19a) (122 mg, 0.38 mmol) using the same two-step procedure described for (21a) to provide the crude product, which was purified by SCX-2 to give the racemate (70 mg). ^1H NMR (300 MHz, CDCl_3) (racemate) δ 1.49-1.73 (m, 3H), 1.89 (m, 2H), 2.43 (s, 3H), 2.62 (t, $J=6.79, 7.15$ Hz, 2H), 2.68-2.78 (m, 1H), 2.83-2.93 (m, 1H), 3.14 (dd, $J=15.43, 5.37$ Hz, 1H), 6.34 (dd, $J=7.73, 1.14$ Hz, 1H), 6.96-7.09 (m, 2H), 7.14-7.21 (m, 3H), 7.45-7.48 (m, 2H). LCMS (12 minute method) $[\text{M}+\text{H}]^+ = 329/331$ @ Rt 5.1 min (90%).

30

Example 17: 1-(3,4-Dichlorophenyl)-3-(3-methylamino-propyl)-3,4-dihydro-1*H*-quinolin-2-one (21d)

This was prepared from (19a) (150 mg, 0.47 mmol) using the same two-step procedure described for (21a) to provide the crude product, which was purified by

SCX-2 to give the racemate (111 mg). ^1H NMR (300 MHz, CDCl_3) (racemate) δ 1.49-1.75 (m, 3H), 1.83 (bs, 1H), 1.85-1.97 (m, 1H), 2.43 (s, 3H), 2.63 (t, $J= 13.56$, 6.59 Hz, 2H), 2.68-2.77 (m, 1H), 2.83-2.94 (m, 1H), 3.13 (dd, $J= 15.45$, 5.28 Hz, 1H), 6.36 (dd, $J= 7.73$, 0.93 Hz, 1H), 6.99-7.11 (m, 3H), 7.20-7.21 (m, 1H), 7.35 (d, $J= 2.26$ Hz, 1H), 7.57 (d, $J= 8.48$ Hz, 1H). LCMS (12 minute method) $[\text{M}+\text{H}]^+ = 363/365$ @Rt 5.4 min (92%).

Example 18: 1-(3-Chlorophenyl)-3-(3-methylamino-propyl)-3,4-dihydro-1*H*-quinolin-2-one (21e)

This was prepared from (19a) (200 mg, 0.63 mmol) using the same two-step procedure described for (21a) to provide the crude product, which was purified by SCX-2 to give the racemate (138 mg). ^1H NMR (300 MHz, CDCl_3) (racemate) δ 1.50-1.77 (m, 3H), 1.89-1.96 (m, 2H), 2.44 (s, 3H), 2.64 (t, $J= 6.89$ Hz, 2H), 2.69-2.78 (m, 1H), 2.84-2.93 (m, 1H), 3.10-3.17 (m, 1H), 6.33-6.36 (m, 1H), 6.97-7.10 (m, 2H), 7.11-7.15 (m, 1H), 7.21-7.24 (m, 2H), 7.37-7.47 (m, 2H). LCMS (12 minute method) $[\text{M}+\text{H}]^+ = 329/331$ @ Rt 5.01 min (90%).

Example 19: 1-(4-Fluorophenyl)-3-(3-methylamino-propyl)-3,4-dihydro-1*H*-quinolin-2-one (21f)

This was prepared from (19a) (200 mg, 0.63 mmol) using the same two-step procedure described for (21a) to provide the crude product, which was purified by SCX-2 to give the racemate (48 mg). ^1H NMR (300 MHz, CDCl_3) (racemate) δ 1.26-1.28 (m, 1H), 1.92 (m, 2H), 2.63 (bs, 1H), 2.72 (m, 1H), 2.85-3.08 (m, 2H), 3.48-3.51 (m, 5H), 6.32-6.34 (d, $J= 7.91$ Hz, 1H), 7.01-7.70 (m, 2H), 7.16-7.19 (d, $J= 7.16$ Hz, 5H), 9.46 (bs, 1H). LCMS (12 minute method) $[\text{M}+\text{H}]^+ = 313$ @ Rt 4.5 min (100%).

Example 20: 1-(4-Ethylphenyl)-3-(3-methylamino-propyl)-3,4-dihydro-1*H*-quinolin-2-one (21g)

This was prepared from (19a) (148 mg, 0.46 mmol) using the same two-step procedure described for (21a) to provide the racemate (61 mg). ^1H NMR (300 MHz, CDCl_3) (racemate) δ 1.25-1.30 (m, 1H), 1.52-1.67 (m, 1H), 1.69-1.80 (m, 2H), 1.87-

1.98 (m, 1H), 2.46 (s, 3H), 2.67-2.92 (m, 9H), 3.11-3.16 (m, 1H), 6.34-6.37 (m, 1H), 6.94-7.06 (m, 2H), 7.09-7.11 (d, $J=8.1$ Hz, 2H), 7.17-7.20 (d, $J=7.35$ Hz, 1H), 7.30-7.33 (d, $J=8.28$ Hz, 2H). LCMS (12 minute method) $[M+H]^+$ = 323 @ Rt 5.4 min (98%).

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Example 21: 3-Methyl-3-(3-methylamino-propyl)-1-p-tolyl-3,4-dihydro-1*H*-quinolin-2-one (21h)

This was prepared from (19b) (806 mg, 2.89 mmol) using the same methods described for (21a) to provide the racemate. The racemate was separated into its individual enantiomers using chiral HPLC. 1H NMR (300 MHz, $CDCl_3$) (racemate & isomer) δ 1.24 (s, 3H), 1.60-1.65 (m, 4H), 2.40 (s, 3H), 2.43 (s, 3H), 2.60-2.65 (m, 2H), 2.87 (d, $J=15.73$ Hz, 1H), 2.98 (d, $J=15.73$ Hz, 1H), 3.46 (br, 1H), 6.30 (dd, $J=7.91, 1.13$ Hz, 1H), 6.90-7.05 (m, 2H), 7.05 (d, $J=8.29$ Hz, 2H), 7.10-7.20 (m, 1H), 7.29 (d, $J=7.91$ Hz, 2H). LCMS (12 minute method) $[M+H]^+$ = 323 @Rt 5.06 min (100%).

Example 22: 1-(4-Chlorophenyl)-3-methyl-3-(3-methylamino-propyl)-3,4-dihydro-1*H*-quinolin-2-one (21i)

This was prepared from (19b) (100 mg, 0.30 mmol) using the same methods described for (21a) to provide the racemate (97 mg). 1H NMR (300 MHz, $CDCl_3$) (racemate) δ ppm 1.25 (s, 3H), 1.55-1.65 (m, 4H), 2.41 (s, 3H), 2.58 (m, 2H), 2.89 (d, $J=15.82$ Hz, 1H), 2.98 (d, $J=15.82$ Hz, 1H), 3.12 (br, 1H), 6.29 (dd, $J=7.91, 0.94$ Hz, 1H), 6.95-7.10 (m, 2H), 7.14 (d, $J=8.67$ Hz, 2H), 7.15 (m, 1H), 7.45 (d, $J=8.67$ Hz, 2H). LCMS (12 minute method) $[M+H]^+$ = 343/345 @Rt 5.09 min (100%).

Example 23: 1-(3,4-Difluorophenyl)-3-methyl-3-(3-methylamino-propyl)-3,4-dihydro-1*H*-quinolin-2-one (21j)

This was prepared from (19b) (100 mg, 0.30 mmol) using the same two-step procedure described for (21a) to provide the crude product, which was purified by SCX-2 to give the racemate (100 mg). 1H NMR (300 MHz, $CDCl_3$) (racemate) δ ppm 1.25 (s, 3H), 1.55-1.65 (m, 4H), 2.41 (s, 3H), 2.50-2.60 (m, 2H), 2.89 (d, $J=$

15.45 Hz, 1H), 2.90 (s, 1H), 2.98 (d, $J = 15.45$ Hz, 1H), 6.30 (dd, $J = 7.91, 1.13$ Hz, 1H), 6.90-7.10 (m, 4H), 7.18 (dd, $J = 7.16, 1.32$ Hz, 1H), 7.22-7.35 (m, 1H). LCMS (12 minute method) $[M+H]^+ = 345$ @Rt 4.85 min (97%).

5 **Example 24: 3-Methyl-3-(3-methylamino-propyl)-1-*m*-tolyl-3,4-dihydro-1*H*-quinolin-2-one (21k)**

This was prepared from (19b) (100 mg, 0.30 mmol) using the same two-step procedure described for (21a) to provide the crude product, which was purified by SCX-2 to give the racemate (90 mg). ^1H NMR (300 MHz, CDCl_3) (racemate) δ

10 ppm 1.26 (s, 3H), 1.50-1.70 (m, 4H), 1.75 (s, 1H), 2.38 (s, 3H), 2.39 (s, 3H), 2.50-2.60 (m, 2H), 2.89 (d, $J = 15.64$ Hz, 1H), 2.98 (d, $J = 15.64$ Hz, 1H), 6.30 (dd, $J = 7.82, 1.04$ Hz, 1H), 6.90-7.07 (m, 4H), 7.18 (dd, $J = 13.66, 7.63$ Hz, 2H), 7.37 (t, $J = 7.63$ Hz, 1H). LCMS (12 minute method) $[M+H]^+ = 323$ @Rt 5.09 min (98%).

15 **Example 25: 1-(3,5-Difluorophenyl)-3-methyl-3-(3-methylamino-propyl)-3,4-dihydro-1*H*-quinolin-2-one (21l)**

This was prepared from (19b) (100 mg, 0.30 mmol) using the same two-step procedure described for (21a) to provide the crude product, which was purified by SCX-2 to give the racemate (95 mg). ^1H NMR (300 MHz, CDCl_3) (racemate) δ

20 ppm 1.26 (s, 3H), 1.50-1.65 (m, 4H), 2.40 (s, 3H), 2.50-2.60 (m, 2H), 2.82 (br, 1H), 2.89 (d, $J = 15.82$ Hz, 1H), 2.97 (d, $J = 15.82$ Hz, 1H), 6.34 (dd, $J = 8.01, 1.04$ Hz, 1H), 6.74-6.83 (m, 2H), 6.83-6.92 (m, 1H), 6.97-7.13 (m, 2H), 7.19 (dd, $J = 7.06, 1.22$ Hz, 1H). LCMS (12 minute method) $[M+H]^+ = 345$ @ Rt 4.87 min, (97%).

25 **Example 26: 6-Chloro-3-(3-methylamino-propyl)-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (21m)**

This was prepared from (20a) (285 mg, 0.8 mmol) using the same two-step procedure described for (21a) to provide the crude product, which was purified by preparative LCMS to give the racemate (62 mg). ^1H NMR (300 MHz, CDCl_3)

30 (racemate) δ 1.49-1.76 (m, 3H), 1.86-1.95 (m, 1H), 2.33 (bs, 1H), 2.44 (s, 3H), 2.61-2.95 (m, 4H), 3.09-3.16 (m, 1H), 6.24-6.27 (d, $J = 8.67$ Hz, 1H), 6.99 (dd, $J =$

8.67, 2.26 Hz, 1H), 7.17-7.19 (m, 3H), 7.39-7.44 (m, 1H), 7.47-7.52 (m, 2H). LCMS (12 minute method) $[M+H]^+$ = 329/331 @ Rt 5.04 min (93%).

5 Example 27: 6-Chloro-1-(4-chlorophenyl)-3-(3-methylamino-propyl)-3,4-dihydro-*1H*-quinolin-2-one (21o)

This was prepared from (20a) (160 mg, 0.45 mmol) using the same two-step procedure described for (21a) to provide the crude product, which was purified by preparative LCMS to give the racemate (52 mg). 1H NMR (300 MHz, $CDCl_3$) (racemate) δ 1.57-1.67 (m, 1H), 1.73-1.75 (m, 2H), 1.87-1.9 (m, 1H), 2.47 (s, 2H), 10 2.64 (s, 1H), 2.68-2.73 (m, 2H), 2.81-2.89 (m, 1H), 3.07-3.13 (m, 3H), 6.27 (d, J = 8.48 Hz, 1H), 7.02 (d, J = 8.48 Hz, 1H), 7.14 (d, J = 8.29 Hz, 2H), 7.19 (s, 1H), 7.47 (d, J = 8.29 Hz, 2H). LCMS (12 minute method) $[M+H]^+$ = 363/365 @ Rt 5.4 min (72%).

15 Example 28: 6-Chloro-3-methyl-3-(3-methylamino-propyl)-1-*p*-tolyl-3,4-dihydro-*1H*-quinolin-2-one (21p)

This was prepared from (20b) (490 mg, 1.34 mmol) using the same methods described for (21a) to provide the racemate (470 mg). The racemate was separated into its individual enantiomers using chiral HPLC. 1H NMR (300 MHz, $CDCl_3$) (racemate) δ 1.25 (s, 3H), 1.50-1.65 (m, 4H), 2.39 (s, 3H), 2.40 (s, 3H), 2.50-2.60 (m, 3H), 2.86 (d, J = 16.01 Hz, 1H), 2.94 (d, J = 16.01 Hz, 1H), 6.24 (d, J = 8.67 Hz, 1H), 6.97 (dd, J = 8.76, 2.35 Hz, 1H), 7.03 (d, J = 8.10 Hz, 2H), 7.14 (d, J = 2.26 Hz, 1H), 7.29 (d, J = 7.91 Hz, 2H); 1H NMR (300 MHz, MeOD-d4) (isomer hemi-D-tartrate salt) δ 1.15 (s, 3H), 1.50-1.75 (m, 4H), 2.32 (s, 3H), 2.51 (s, 3H), 2.78 (br, 2H), 2.84 (d, J = 16.20 Hz, 1H), 2.98 (m, 1H), 3.15-3.25 (m, 2H), 4.22 (s, 1H), 6.14 (d, J = 8.85 Hz, 1H), 6.90-6.70 (m, 3H), 7.19 (d, J = 2.26 Hz, 1H), 7.25 (d, J = 7.91 Hz, 2H). LCMS (12 minute method) $[M+H]^+$ = 357/359 @Rt 5.43 min (100%).

30 Example 29: 6-Chloro-1-(4-chlorophenyl)-3-methyl-3-(3-methylamino-propyl)-3,4-dihydro-*1H*-quinolin-2-one (21q)

This was prepared from (20b) (490 mg, 1.34 mmol) using the same methods described for (21a) to provide the racemate (425 mg). 1H NMR (300 MHz, $CDCl_3$)

(racemate) δ ppm 1.25 (s, 3H), 1.50-1.65 (m, 4H), 2.39 (s, 3H), 2.40 (br, 1H), 2.50-2.60 (m, 2H), 2.87 (d, J = 16.20 Hz, 1H), 2.95 (d, J = 16.20 Hz, 1H), 6.23 (d, J = 8.85 Hz, 1H), 7.00 (dd, J = 8.57, 2.35 Hz, 1H), 7.05-7.20 (m, 3H), 7.40-7.50 (m, 2H). LCMS (12 minute method) $[M+H]^+$ = 377/379 @Rt 5.26 min (94%).

5

Example 30: 3-Methyl-3-(3-methylamino-propyl)-1-thiophen-2-yl-3,4-dihydro-1H-quinolin-2-one (22a)

This was prepared from (19b) (200 mg, 0.60 mmol) using the same two-step procedure described for (21a) to provide the crude product, which was purified by 10 SCX-2 to give the racemate (125 mg). 1H NMR (300 MHz, $CDCl_3$) (racemate) δ ppm 1.25 (s, 3H), 1.50-1.65 (m, 4H), 2.39 (s, 3H), 2.50-2.60 (br, 2H), 2.88 (d, J = 16.20 Hz, 1H), 2.97 (d, J = 16.20 Hz, 1H), 3.17 (br, 1H), 6.58 (dd, J = 8.01, 0.85 Hz, 1H), 6.89 (dd, J = 3.58, 1.32 Hz, 1H), 6.95-7.15 (m, 3H), 7.16 (d, J = 7.16 Hz, 1H), 7.32 (dd, J = 5.65, 1.32 Hz, 1H). LCMS (12 minute method) $[M+H]^+$ = 315 @Rt 15 4.35 min (98%).

Example 31: 3-Methyl-3-(3-methylamino-propyl)-1-thiophen-3-yl-3,4-dihydro-1H-quinolin-2-one (22b)

This was prepared from (19b) (200 mg, 0.60 mmol) using the same two-step 20 procedure described for (21a) to provide the crude product, which was purified by SCX-2-2 to give the racemate (128 mg). 1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.50-1.65 (m, 4H), 2.40 (s, 3H), 2.50-2.60 (m, 2H), 2.87 (d, J = 15.82 Hz, 1H), 2.96 (d, J = 15.82 Hz, 1H), 3.07 (br, 1H), 6.45 (dd, J = 8.10, 0.94 Hz, 1H), 6.92 (dd, J = 5.09, 1.32 Hz, 1H), 6.98 (td, J = 7.35, 1.13 Hz, 1H), 7.07 (td, J = 7.77, 1.60 Hz, 25 1H), 7.16 (d, J = 7.35 Hz, 1H), 7.22 (dd, J = 3.20, 1.32 Hz, 1H), 7.41 (dd, J = 5.09, 3.20 Hz, 1H). LCMS (12 minute method) $[M+H]^+$ = 315 @Rt 4.29 min (100%).

Method D

30

Preparation of intermediates

{3-[1-(4-Methoxy-benzyl)-3-methyl-2-oxo-6-phenyl-1,2,3,4-tetrahydro-quinolin-3-yl]-propyl}-methyl-carbamic acid *tert*-butyl ester (23)

Step (i)

Sodium hydride (340 mg, 60% dispersion in mineral oil, 8.55 mmol, 1.3 eq.) was
5 added portionwise to a soln of (20c) (2.7 g. 6.57 mmol) in DMF (40 mL) at 0°C. The reaction mixture was left for 30 min at this temperature and then 4-methoxybenzyl chloride (1.16 mL, 8.55 mmol, 1.3 eq.) in DMF (1 mL) was added dropwise over 10 min. The reaction mixture was warmed to rt slowly and after 1 h was poured into ethyl acetate (200 mL) and extracted with water (3 x 50 mL). The
10 organic layer was separated, dried over MgSO₄ and concentrated under vacuo. The crude product was purified using automated chromatography (silica) (0 to 80% ethyl acetate\cyclohexane gradient) to provide the 4-methoxybenzyl protected 6-bromo precursor (2.2 g, 63%).

Step (ii)

15 The product from Step (i) (100 mg, 0.23 mmol), phenylboronic acid (85 mg, 0.70 mmol, 3 eq.), K₂CO₃ (138 mg, 1 mmol, 4.3 eq.) and Pd(PPh₃)₄ (11 mg, 0.009 mmol, 0.04 eq.) were suspended in ethanol (1 mL) and water (0.6 mL). The reaction mixture was heated at 80°C overnight, cooled to rt and filtered through celite. The filtrate was poured into ethyl acetate (100 mL) and water (50 mL) and extracted.
20 The organic layer was separated, dried over MgSO₄ and concentrated to provide the product (23) (120 mg, 98%) that was used without further purification.

Methyl-[3-(3-methyl-2-oxo-6-phenyl-1,2,3,4-tetrahydro-quinolin-3-yl)-propyl]-carbamic acid *tert*-butyl ester

25 **Step (iii) & (iv)**

A mixture of (23) (120 mg, 0.23 mmol) and anisole (25 μL, 0.23 mmol) in trifluoroacetic acid (2.3 mL) was heated at 65°C under nitrogen for 4 h. The reaction mixture was concentrated under vacuo and the residue was dissolved in methanol (2 mL). The methanol soln was applied to an SCX-2 column (5g) and the column
30 washed with methanol (50 mL). The product was eluted with 2N Et₃N in methanol (50 mL) and the basic soln was concentrated to provide 3-Methyl-3-(3-methylamino-propyl)-6-phenyl-3,4-dihydro-1*H*-quinolin-2-one (72 mg, 100%). To a

soln of this amine (72 mg, 0.23 mmol) in anhydrous THF (2 mL) at 0°C was added di-*tert*-butyl dicarbonate (53 mg, 97%, 0.24 mmol) in one portion. The reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was poured into ethyl acetate (25 mL) and water (10 mL) and extracted. The organic layer was
5 separated, dried over MgSO₄ and concentrated to give the Boc protected precursor (95 mg, 100%). This material was used without further purification.

Examples

10 Example 32: 3-Methyl-3-(3-methylamino-propyl)-6-phenyl-1-*p*-tolyl-3,4-dihydro-1H-quinolin-2-one (24)

This was prepared from the above Boc protected precursor (95 mg, 0.23 mmol) using the same two-step procedure described for Method C (19a to 21a) to provide the crude product, which was purified by SCX-2 to give the racemate (53 mg).

15 ¹H NMR (300 MHz, CDCl₃) (racemate) δ 1.29 (s, 3H), 1.50-1.70 (m, 4H), 2.42 (s, 6H), 2.55-2.65 (m, 2H), 2.94 (d, J= 15.64 Hz, 1H), 3.04 (d, J= 15.64 Hz, 1H), 3.18 (br, 1H), 6.38 (d, J= 8.29 Hz, 1H), 7.09 (d, J= 8.10 Hz, 2H), 7.29 (m, 4H), 7.41 (m, 3H), 7.54 (m, 2H). LCMS (12 minute method) [M+H]⁺ = 399 @Rt 6.06 min (100%):

20 The pharmacological profile of the present compounds may be demonstrated as follows.

Scintillation proximity assays for determining the affinity of test ligands at the norepinephrine transporter.

25 The compounds of the invention are norepinephrine reuptake inhibitors, and possess excellent activity in, for example, a scintillation proximity assay (e.g. J. Gobel, D.L. Saussy and A. Goetz, J. Pharmacol. Toxicol. (1999), 42, 237-244). Thus ³H-nisoxetine binding to norepinephrine re-uptake sites in a cell line transfected with human norepinephrine transporter binding has been used to
30 determine the affinity of ligands at the norepinephrine transporter.

Acid Stability

The acid stability of a compound according to the present invention was determined as a solution in buffer at 6 different pH values (HCl 0.1N, pH 2, pH 4, pH 6, pH 7, and pH 8) at 40°C over a time course of 72 hours. Samples were taken at the beginning of the study and after 3, 6 and 24 hours and analysed by capillary electrophoresis. The original sample used in this study contained 0.8% of the undesired epimer as internal standard. The samples taken at the different time points during the study did not show any significant change in the percentage of the undesired epimer. This confirms that the compound is chemically and configurationally stable under acidic conditions.

15 In Vitro Determination of the Interaction of compounds with CYP2D6 in Human Hepatic Microsomes

Compounds preferably do not interact with CYP2D6

20 **Principle:**

The interaction of compounds with CYP2D6 was evaluated by the measurement of the inhibition of the bufuralol 1-hydroxylase activity by the compounds.

25 **Assay description:**

Bufluralol 1-hydroxylase activity is determined by using 0.5 mg/ml human liver microsomal protein (human biologics), 10 µmol/L bufluralol, in 0.1 M sodium phosphate buffer pH 7.4, incubated for 5 min at 37°C in the presence of 2 mM β-NADPH, with 0, 5 or 25 µM of the test compound (inhibitor). The compound was dissolved in acetonitrile, such that the final concentration of acetonitrile in the incubation was 0.5%. The total reaction volume was 100 µl. The reaction was terminated by addition of 75 µl of methanol followed by centrifugation. 40 µl of the supernatant was analysed by HPLC.

Analysis conditions:

A Beckman Ultrasphere C₁₈ column (5 μm, 250 x 4.6 mm) was used, with a 13 minute gradient from 100% of solvent A (0.02 M potassium dihydrogen phosphate buffer pH 3/methanol (65/35)) to 100 % of solvent B (0.02 M potassium dihydrogen phosphate buffer pH 3/methanol (20/80)), according to the following gradient. The run time was 20 minutes. Formation of 1'-hydroxybufuralol was detected by fluorimetric detection with extinction at λ 252 nm and emission at λ 302 nm.

| Time (min) | Solvent A (%) | Solvent B (%) |
|------------|---------------|---------------|
| 0 | 100 | 0 |
| 8 | 0 | 100 |
| 12 | 0 | 100 |
| 13 | 100 | 0 |

Calculation of the results:

The percent of inhibition is calculated as follows:

$$100 - \frac{100 \times 1\text{-hydroxybufuralol area formed with inhibitor}}{1\text{-hydroxybufuralol area formed without inhibitor}}$$

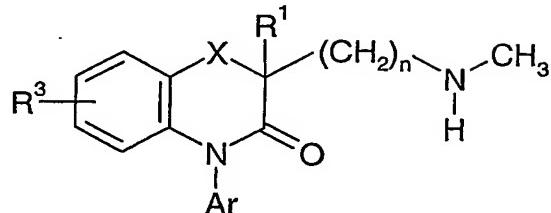
The IC₅₀ is calculated from the percent inhibition as follows (assuming competitive inhibition): $\frac{\text{Compound Concentration} \times (100 - \text{Percent of inhibition})}{\text{Percent of inhibition}}$

20

The IC₅₀ estimation is assumed valid if inhibition is between 20% and 80% (Moody 1999).

CLAIMS

1. A compound of formula (I)



5

(I)

wherein

-X- is -C(R⁴R⁵)-, -O- or -S-;

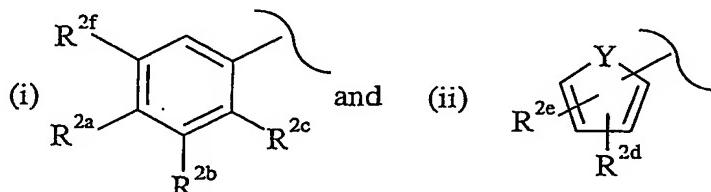
n is 2 or 3;

R¹ is H or C₁-C₄ alkyl;

10 R³ is H, halo, C₁-C₄ alkyl, O(C₁-C₄ alkyl), nitrile, phenyl or substituted phenyl;

R⁴ and R⁵ are each independently selected from H or C₁-C₄ alkyl;

Ar- is selected from the group consisting of



15

in which

R^{2a} is H, halo, methyl or ethyl;

R^{2b} is H, halo or methyl;

R^{2c} is H, halo, methyl, trifluoromethyl, nitrile or methoxy;

R^{2d} is H, halo, methyl or ethyl;

20 R^{2e} is H, halo, methyl, trifluoromethyl, nitrile or methoxy;

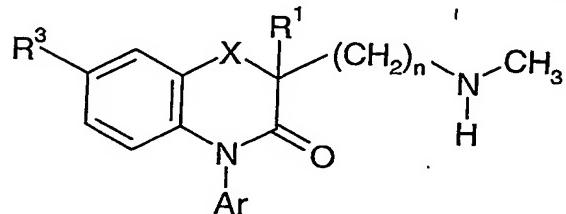
R^{2f} is H, or fluoro;

-Y- is -O-, -S- or -N(R⁶)-; and

R⁶ is H or methyl;

and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1, represented by the formula (Ia)



5

(Ia)

wherein $-\text{X}-$, n , R^1 , R^3 and Ar have the values as defined for formula (I) in claim 1.

3. A compound as claimed in either claim 1 or 2, wherein $-\text{X}-$ is
10 $-\text{C}(\text{R}^4\text{R}^5)-$.

4. A compound as claimed in claim 3, wherein R^4 and R^5 are both H.

- 15 5. A compound as claimed in claim 3, wherein R^4 and R^5 are both the same $\text{C}_1\text{-C}_4$ alkyl.

6. A compound as claimed in any one of claims 1 to 5, wherein Ar is
20 (i).

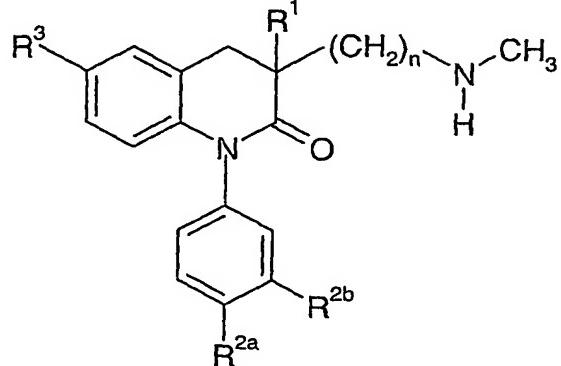
7. A compound as claimed in claim 6, wherein R^{2c} is H.

- 25 8. A compound as claimed in either claim 6 or 7, wherein R^{2a} is H or methyl, R^{2b} is H and R^{2f} is H.

9. A compound as claimed in either claim 6 or 7, wherein R^{2a} is H, R^{2b} is halo and R^{2f} is H or fluoro.

10. A compound as claimed in any one of claims 1 to 5, wherein Ar is (ii) and -Y- is -S-.

5 11. A compound as claimed in any one of claims 1 to 4, represented by the formula II



(II)

wherein n, R¹, R^{2a} and R^{2b} have the values as defined for formula (I) in claim 1 and R³ is H, halo, phenyl or substituted phenyl.

10

12. A compound as claimed in any one of claims 1 to 11, wherein n is 3.

13. A compound as claimed in any one of claims 1 to 12, wherein R¹ is H, methyl, ethyl or n-propyl.

15

14. A compound as claimed in any one of claims 1 to 13, wherein R³ is H or halo.

20

15. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

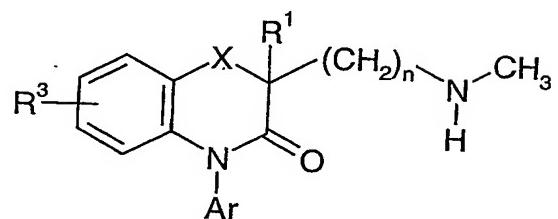
16. A compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof, for use in therapy.

17. Use of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a disorder of the nervous system.
- 5 18. Use as claimed in claim 17 wherein the disorder of the nervous system is selected from the group consisting of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder (ADD) due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, mania, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, TIC disorders, cognitive disorders including mild cognitive impairment (MCI), dementia of the Alzheimers type (DAT), vascular dementia and cognitive impairment associated with schizophrenia (CIAS), hypotensive states including orthostatic hypotension, and pain including chronic pain, neuropathic pain and antinociceptive pain.
- 10 19. A method for selectively inhibiting the reuptake of norepinephrine in mammals, comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof.
- 15
- 20
- 25
- 30

20. A method for treating disorders associated with norepinephrine dysfunction in mammals, comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof.

ABSTRACT

This invention relates to compounds of formula (I)



5 where -X-, n, R¹, R³ and Ar- have the values defined in claim 1, their preparation and use as pharmaceuticals.